THE JOURNAL OF
PEDIATRICS

NOVEMBER 1961 *Volume* 59 *Number* 5

# *Mellituria, a paper chromatographic study*

**Horst Bickel, M.D., Ph.D.***

MARBURG, GERMANY

UNTIL recently the study of the various forms of mellituria has been neglected, despite the active interest that has been shown in other fields of metabolic research. General surveys of the subject are scanty,[1-7] and certain inborn errors of sugar metabolism, such as idiopathic galactosemia, pentosuria, and fructose intolerance, have attracted general interest only in the last few years. Yet as far back as 1911 Hoeniger[8] and Nothmann[9] observed mellituria in newborn and premature infants, and at about the same time v. Reuss,[10] Rietschel,[11] and Mayerhofen[12] drew attention to the excretion of lactose and sucrose in the urine of infants with diarrhea.

The slow progress in this field is largely due to the fact that sufficiently sensitive and specific methods were not available to the clinician for testing the urine of his patients for various sugars on a broad scale. The usual reducing agents, such as the Benedict test, give conclusive results only at sugar concentrations above 150 mg. per 100 ml. and react with various other oxidizing agents such as ascorbic acid, uric acid, creatinine, homogentisic acid, glucuronides, salicylates, and hydrazine derivatives. Sucrose, on the other hand, has no reducing power. More specific methods for sugar identification, such as optical rotation, formation of osazon crystals, yeast fermentation, and the Seliwanoff, mucic acid, Bial, diphenylhydrazine, and naphthoresorcinol tests are laborious and unreliable, if the sugar is present in small quantities or combined with other sugars. As late as 1950 Lasker[13] recommended a schema for the diagnosis of unidentified sugars in the urine which is so involved as to be beyond the scope of most clinical laboratories.

*From the Department of Pediatrics (Director: Prof. Dr. F. Linneweh), University of Marburg, Germany.*

**Address, Universitäts—Kinderklinik, Deutschhausstrasse 12 Marburg/Lahn, Germany.*

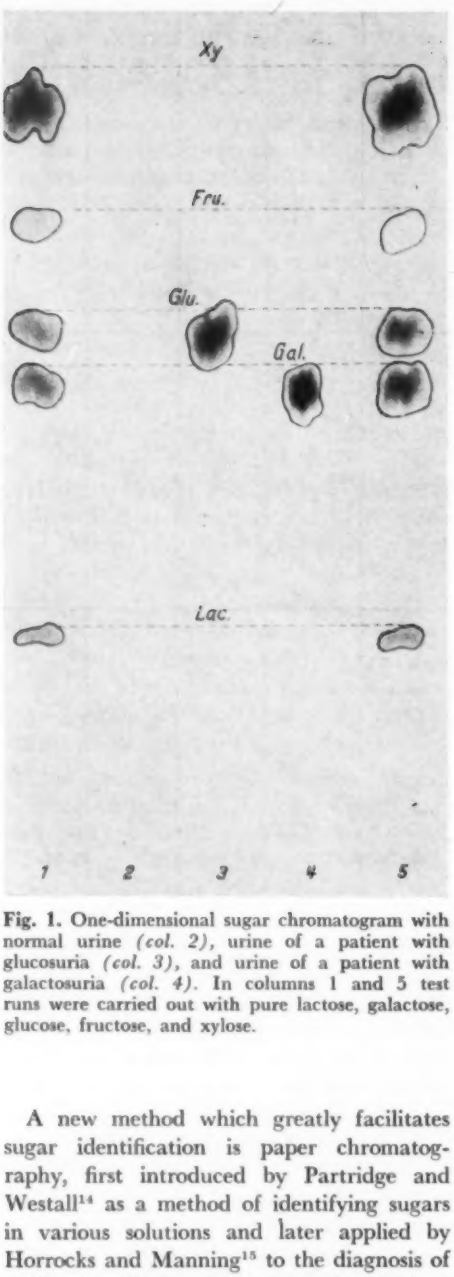



**Fig. 1.** One-dimensional sugar chromatogram with normal urine *(col. 2)*, urine of a patient with glucosuria *(col. 3)*, and urine of a patient with galactosuria *(col. 4)*. In columns 1 and 5 test runs were carried out with pure lactose, galactose, glucose, fructose, and xylose.

A new method which greatly facilitates sugar identification is paper chromatography, first introduced by Partridge and Westall[14] as a method of identifying sugars in various solutions and later applied by Horrocks and Manning[15] to the diagnosis of mellituria. The one-dimensional technique suffices for the limited number of sugars generally found in the urine. It is quicker and cheaper than two-dimensional methods and separates the various sugars satisfactorily. The loss of substances during the run is slight, and a dozen specimens and 3 test sugar mixtures can be run at the same time on one sheet of filter paper. After the development of the paper the sugar concentration can be assessed with an average range of about 15 per cent error, and though this range is too large for exact quantitative work, the results are sufficiently accurate for most clinical purposes. Moreover, the specificity of the method compares favorably with that of other so-called quantitative methods; it is also highly sensitive, as most sugars can be identified in concentrations of less than 10 mg. per 100 ml. urine.

During the last 8 years we have applied sugar chromatography in the research laboratories of the University Children's Hospitals in Birmingham, England, and in Marburg, Germany, to a variety of clinical problems. [7, 16-20] The present communication gives a short description of the method and summarizes the chromatographic results of a study of the following 3 aspects of mellituria.

1. The sugar excretion of healthy infants, premature infants, healthy toddlers, and school children.

2. The sugar excretion of 1,000 patients suffering from various disorders possibly connected with disturbances of sugar and/or amino acid metabolism.

3. In a limited group of healthy children and healthy adults and of patients suffering from diseases of the liver, kidney, and the intestinal tract the sugar excretion was measured in the fasting state and at regular intervals after a sugar loading test.

A comparison of the results of the chromatographic investigations with those of a reduction test (Benedict's test) reveals the severe limitations of this traditional reduction method in the recognition and identification of the various melliturias.

## METHOD

The urine specimens were collected under chloroform and toluol and were stored in a refrigerator at +4° C. for short intervals, or at –20° C. if in exceptional cases the chromatographic run could not be started

within the next day or two. From the healthy infants and premature ones 24-hour collections were available, while the urine specimens of most of the other patients and of the healthy controls were early morning fasting samples. During the sugar loading tests a fasting specimen was taken immediately before the loading and further samples at 1, 2, and 3 hours after the ingestion of sugar.

Each urine was subjected to the Benedict reduction test by boiling 5 ml. of the reagent with 8 drops of urine for 5 minutes in a water bath, shaking the test tube and describing the final color reaction. The urine volume used for each chromatogram was chosen according to the color reaction of the Benedict test, 100 μl being taken on a blue reaction, 50 μl on a green reaction, 20 μl on a yellow reaction, and 10 μl on a red reaction.

The urines were then desalted by the resin method described by Partridge and Westall[14] and modified by Woolf,[21] with the use of the anion and cation exchanger "Bio-Deminrolit."* This desalting procedure is quick and simple and leads to no perceptible loss of sugar in the urine.

For the sugar partition we use Whatman filter paper No. 4 or Paper No. 2040 from Schleicher and Schüll, which has similar qualities. The 57 by 46 cm. sheets of the latter make are divided by pencil marks into 15 columns.[18] For test purposes 3 mixtures of pure sugars of different strengths are pipetted onto columns 1, 8, and 15, mixture I contained in 20 μl distilled water. 10 gamma each of galactose, glucose and xylose and 30 gamma each of lactose and fructose; mixture II in 20 μl 20 gamma galactose, glucose, and xylose, and 60 gamma each of lactose and fructose; mixture III in 20 μl 30 gamma each of galactose, glucose, and xylose, and 90 gamma each of lactose and fructose. The remaining 12 columns are used for urine samples. To ensure that the speed of the chromatographic run is identical with that of the test sugar solutions, a fast traveling test sugar, ribose, is added in a quantity of 20 gamma in 20 μl distilled water to each run and its final position on the paper is compared in the different columns.

The actual run is done by the descending technique in a wooden box placed in a thermostatically controlled room at a temperature of 20 to 25° C. with a range of temperature not exceeding ±1° C. The solvent is made up of 60 vol. N-butanol, 16.5 vol. ethanol, 40 vol. distilled water, and 1 vol. of a mixture of 3.2 ml. concentrated ammonium hydroxyde and 96.8 ml. distilled water. After the run the paper is dried and sprayed with aniline phthalate which develops all sugars in quantities from 5 to 10 gamma upward with the exception of fructose, other ketoses, and lactose, which show up only from quantities of 20 to 40 gamma upward; sucrose gives a weak color reaction from 50 gamma on. For the detection of lower concentrations of ketoses, a duplicate paper chromatogram should be sprayed with the naphthoresorcinol reagent. In the present study this spray was used as a routine in the sugar loading experiment but only occasionally in the other investigations, so that small amounts of ketoses, especially of sucrose, may have been overlooked.

A chromatogram with urines of a healthy control, a patient with glucosuria and a patient with galactosuria, respectively, is reproduced in Fig. 1. The unknown sugars are identified by comparing their location with the test sugars on the same paper or by measuring their rate of flow (Rf) values. Where the solvent front is allowed to overflow, these values cannot be related to the solvent front but only to the front of the test sugar ribose according to the formula:

$$\text{Rf ribose} = \frac{\text{distance of the unknown sugar from origin}}{\text{distance of ribose from origin}}$$

Table I gives such Rf values for some of the more common sugars. A semiquantitative evaluation of the sugar concentration in the urine was carried out by comparing size and color intensity of the sugar spots of unknown quantity with the test sugar spots in column

*Permutit Company Ltd.

**Table I.** Rf values of various sugars related to ribose (Rf = 1.0) (solvent as described in the text)

| | *Average in 20 chromatograms* | *Range* | *Color in aniline phthalate* | *Color in naphthoresorcinol* |
|---|---|---|---|---|
| Rhamnose | 1.24 | 1.20 to 1.28 | Brown | |
| Xylose | 0.89 | 0.87 to 0.92 | Pink | |
| Mannose | 0.81 | 0.77 to 0.83 | Brown | |
| Arabinose | 0.77 | 0.75 to 0.81 | Pink | |
| Fructose | 0.75 | 0.72 to 0.80 | Brown | Red-yellow |
| Glucose | 0.64 | 0.60 to 0.67 | Brown | |
| Galactose | 0.59 | 0.56 to 0.64 | Brown | |
| Sucrose | 0.42 | 0.38 to 0.50 | Pale brown | Red-yellow |
| Maltose | 0.32 | 0.27 to 0.43 | Brown | |
| Lactose | 0.29 | 0.25 to 0.41 | Brown | |
| Fructuronic acid | 0.25 | 0.19 to 0.36 | Pink | |
| Galacturonic acid | 0.22 | 0.17 to 0.33 | Pink | |

1, 9, or 15 of known quantity. If the urine sugar concentration was higher than that of the test sugars, smaller volumes and, if necessary, various dilutions of the urine were rechromatographed until the urine sugar concentration fitted into the range of the test sugars. The error of this method lies at about 15 per cent, which is admissible for the scope of our investigation.

**Sugar excretion in the urine of healthy infants and children.** The sugar excretion was examined in 155 twenty-four–hour urine collections from 88 mature infants and in 55 collections from 16 premature ones. The average sugar excretion during the first 6 weeks is shown in Table II; after this age the sugar excretion in the urine is negligible and does not differ significantly from that of older children. The values are expressed as milligrams per 100 ml. urine, though the 24-hour urine volumes are also recorded. The urine volume varied considerably from day to day, from case to case, and between full-term and premature infants; if related to the sugar concentration of the urine, it introduces a new and very variable factor in the assessment of the mellituria of this age group.

Infants born at term exhibit a physiologic mellituria which lasts for the first 10 days and reaches its maximum on the third, fourth, or fifth day. The concentration of fructose and glucose is relatively high from the beginning, while the concentrations of lactose and galactose increase when milk feeding starts. The highest values recorded are for lactose 150 mg., for fructose 70 mg., for galactose 25 mg., and for glucose 25 mg. per 100 ml. After the second week of life occasional traces of lactose, galactose, and glucose are found in the urine, but they do not exceed 10 mg. per 100 ml.

Premature infants have an even greater mellituria, mainly on account of a higher fructose and lactose concentration in the urine (Table II). While most premature infants normalize the sugar excretion in the second week of life, exceptions to this rule are more frequent than in full-term infants.

The sugar excretion after infancy was tested in early morning specimens from 10 healthy toddlers, 100 school children, and 15 healthy adults. Only 8 of the 125 urines showed traces of sugars, in which 7 cases consisted of 10 mg. per 100 ml. or less of glucose and, in one case, of 10 mg. per 100 ml. each of glucose and galactose.

*Comment.* Only few chromatographic studies have been published where the method and conditions permit a critical comparison with our own results. In 24 of 50 full-term infants and 20 of 26 premature ones Haworth[22] found increased amounts of galactose, lactose, glucose, and occasionally xylose in the urine; fructose was not mentioned. Similar data were recorded by Woolf[23] and by Apthorp,[24] who stresses the influence of milk feeding on the galactose and lactose excretion in the urine. Our earlier investigations of single urine specimens from 68 newborn infants during the first 9 days of life[18] gave the results listed in Table III.

The figures represent average sugar concentrations in milligrams per 100 ml.; the

figures in parentheses are the maximal concentrations observed for each sugar. The values agree reasonably well with those in Table II, though less fructose was found in this earlier study.

It is possible that different feeding schedules may affect the mellituria in young infants and may render a comparison between the results of individual workers difficult. In our recent group of infants (Table II) it was not possible to apply an uniform feeding schedule to all infants tested, though all premature infants received human milk for the first 3 weeks of life. Some of them were then gradually weaned to a two-thirds acidified cow's milk formula with addition of 5 per cent sucrose or dextromaltose and 2 per cent flour. Full-term infants were sometimes weaned to a similar formula during the second week. Our data do not enable us to state whether infants fed on cow's milk vary in the urinary sugar pattern from those who are breast fed.

The sugar excretion of healthy individuals beyond infancy has been studied by enzymatic methods[1] and by chromatography.[18, 23-26] Traces of up to 15 mg. glucose per 100 ml. urine have been observed repeatedly, while still smaller traces of galactose have been detected only very occasionally. On a diet rich in milk, lactose was frequently observed in concentrations up to 35 mg. per 100 ml. Other sugars such as sucrose, fructose, xylose, and arabinose were likewise found to be affected by the dietary intake and may appear in concentrations up to 10 and occasionally up to 30 mg. per 100 ml. if the diet is rich in fruit and vegetables. This observation agrees well with the results of our loading tests, while the scanty sugar yield in the urine investigations mentioned earlier may be due to the fact that early morning fasting specimens were used.

It is intriguing to speculate about the mechanism of the mellituria of the newborn. It can be assumed, in view of the rather low

**Table II.** Sugar excretion in the urine during the first 6 weeks of life (expressed in mg./100 ml. as mean value (M) and standard deviation ($\pm \sigma$ M)*

| *Age* | *No. of urines* | *Fructose* | *Galactose* | *Glucose* | *Lactose* | *Sum of 4 sugars* | *Average of 24-hour urine volume (ml.)* |
|---|---|---|---|---|---|---|---|
| *Mature infants* | | | | | | | |
| 1 day | 16 | 23.1 ± 8.0 | 0 | 10.9 ± 3.3 | 10.6 ± 4.5 | 44.6 | 18 |
| 3 days | 15 | 13.3 ± 3.8 | 8.6 ± 1.6 | 10.0 ± 1.2 | 48.2 ± 26.6 | 80.1 | 52 |
| 5 days | 11 | 16.2 ± 3.8 | 9.1 ± 1.6 | 8.6 ± 1.0 | 35.1 ± 8.9 | 69.0 | 94 |
| 7 days | 10 | 3.0 ± 3.0 | 6.3 ± 3.4 | 6.3 ± 1.3 | 23.6 ± 7.9 | 39.2 | 143 |
| 10 days | 8 | 0 | 3.7 ± 1.9 | 1.3 ± 1.3 | 7.5 ± 5.0 | 12.5 | 166 |
| 14 days | 10 | 0 | 3.0 ± 1.5 | 1.0 ± 1.0 | 0 | 4.0 | 210 |
| 21 days | 6 | 0 | 1.4 ± 0.5 | 3.0 ± 1.9 | 0 | 4.4 | 285 |
| 28 days | 3 | 0 | 0 | 0 | 0 | 0 | 310 |
| 6 weeks | 5 | 0 | 1.0 ± 0.7 | 4.0 ± 2.5 | 0 | 5.0 | 270 |
| *Premature infants* | | | | | | | |
| 1 day | Insufficient specimens available | | | | | | |
| 3 days | 5 | 48.1 ± 17.9 | 8.0 ± 2.0 | 11.0 ± 1.0 | 66.0 ± 50.0 | 133.1 | 32 |
| 5 days | 5 | 26.0 ± 3.5 | 2.0 ± 2.0 | 20.0 ± 4.5 | 56.0 ± 11.7 | 104.0 | 40 |
| 7 days | 6 | 18.3 ± 12.1 | 5.9 ± 2.7 | 5.9 ± 2.7 | 25.0 ± 9.4 | 55.1 | 74 |
| 10 days | 7 | 0 | 4.3 ± 2.0 | 1.4 ± 1.4 | 4.3 ± 4.3 | 10.0 | 98 |
| 14 days | 9 | 0 | 0 | 4.0 ± 2.9 | 7.7 ± 8.0 | 11.7 | 120 |
| 21 days | 5 | 0 | 2.5 ± 2.5 | 6.0 ± 5.5 | 7.5 ± 4.1 | 16.0 | 155 |
| 28 days | 7 | 0 | 2.9 ± 1.9 | 7.1 ± 1.3 | 8.5 ± 3.9 | 18.5 | 187 |
| 6 weeks | 8 | 0 | 2.5 ± 1.7 | 4.4 ± 2.2 | 1.3 ± 1.3 | 8.2 | 225 |

*The results in this table and in Tables IX to XI are not strictly quantitative but include errors up to 15 per cent. After the first week of life several mean values in the lower sugar concentrations are not representative; this is probably due to the small number of cases and the large individual variation. The trend of the mean values nevertheless justifies the conclusions given in the text.

**Table III**

| | *No.* | *Lactose* | *Galactose* | *Glucose* | *Fructose* |
|---|---|---|---|---|---|
| Full-term newborn infants | 53 | 19 (100) | 6.7 (30) | 5.5 (30) | 3.2 (30) |
| Premature infants | 15 | 42 (90) | 4.7 (20) | 3.7 (20) | – – |

blood sugar levels of this age period, that the glucosuria is probably and the lactosuria is certainly of prerenal origin. It is most likely that the lactosuria is due to a lactase deficiency and to an increased permeability of the newborn infant's intestinal wall. Fructosuria and galactosuria are often found in liver disease and point to functional immaturity of this organ in the newborn. There are thus probably at least 3 organs involved in this mellituria. Finally, it is of interest to note that the physiologic mellituria disappears within the first fortnight, long before the aminoaciduria, which decreases to a normal amino acid output only after the sixth month of life (Table IV). The tubular reabsorption system for glucose seems to mature more quickly than that for the amino acids, and there seems to be no close correlation between these 2 systems.

**Sugar excretion in 1,000 patients.** Our aim was to obtain a general idea of the sugar pattern in the urine of patients suffering from various disorders. Most urines were submitted for examination because of a positive Benedict test or because aminoaciduria or mellituria was suspected on clinical grounds, so the case material was preselected. In most instances fasting urine specimens were used, and consequently some milder melliturias may have remained undetected.

Of the 1,000 patients, 130 showed an increase in sugar excretion, which in 97 cases amounted to more than 100 mg. per 100 ml. (Fig. 2). In 114 instances the mellituria was due to the isolated increase of a single sugar, predominantly of glucose (77 cases), while isolated lactosuria, fructosuria, and galactosuria were encountered in 13, 12, and 11 cases, respectively. One apparently healthy Jewish girl exhibited congenital xyloketosuria; the urine showed a positive Benedict test; she had been treated repeatedly for diabetes. In 16 instances the mellituria was more generalized, consisting usually of an increase of lactose, galactose, glucose, and fructose with a total sugar concentration exceeding 100 mg. per 100 ml.

The disorders in which these isolated or

**Table IV.** Alpha amino nitrogen excretion in urine of mature and premature infants (gasometric ninhydrin method)

| | | $\alpha$ *AN (mg./kg./24 hr.)** | | | $\frac{\alpha \text{ AN (mg. \%)} \times 100}{\text{NPN (mg. \%)}}$ | |
|---|---|---|---|---|---|---|
| | *Age* | *No.* | $M \pm \sigma M$ | *C* | $M \pm \sigma M$ | *C* |
| *Infants born at term* | | | | | | |
| $I_1$ | 3 to 7 days | 17 | 2.66 ± 0.19 | 29.14 | 2.61 ± 0.16 | 24.84 |
| $I_2$ | 10 to 21 days | 9 | 3.47 ± 0.25 | 20.23 | 2.66 ± 0.25 | 26.27 |
| $I_3$ | 6 to 12 weeks | 9 | 4.96 ± 0.36 | 20.35 | 1.60 ± 0.15 | 26.20 |
| $I_4$ | 6 to 12 months | 9 | 3.38 ± 0.26 | 18.88 | 1.01 ± 0.08 | 22.27 |
| *Premature infants* | | | | | | |
| $P_1$ | 3 to 7 days | 7 | 3.21 ± 0.53 | 40.31 | 2.63 ± 0.31 | 28.57 |
| $P_2$ | 10 to 21 days | 10 | 4.91 ± 0.62 | 38.06 | 4.28 ± 0.52 | 36.17 |
| $P_3$ | 6 to 8 weeks | 5 | 7.38 ± 1.52 | 29.09 | 2.73 ± 0.43 | 22.46 |

*Concerning the alpha amino nitrogen excretion in milligrams per kilogram per 24 hours the differences between the M values are significant ($p < 0.05$) for $I_1 : I_2$, $I_2 : I_3$, and $I_3 : I_4$, not significant ($p > 0.05$) for $P_1 : P_2$ and $P_2 : P_3$. As regards the alpha amino nitrogen coefficients the differences between $I_1 : I_3$, $I_3 : I_4$, $P_1 : P_2$, and $P_2 : P_3$ are significant ($p < 0.05$), between $I_1 : I_2$ insignificant ($p > 0.8$).

generalized mellituras were observed are listed in Table V. Isolated glucosuria was found in all cases of diabetes mellitus and cystinosis but less regularly in the other conditions, most of which showed an involvement of tubular or hepatic function. Isolated lactosuria occurred predominantly in diseases of the intestinal tract and in 2 of 6 cases of hiatus hernia, while isolated fructosuria was always associated with severe liver damage, except in one case of congenital fructose intolerance.[27] As a rule, the mellituria of liver disease (cirrhosis, hepatitis) is generalized with a simultaneous excretion of galactose, glucose, fructose, and sometimes lactose. The same pattern has been encountered in septicemia, toxic gastroenteritis, and in 2 cases of severe rickets and may also be due to secondary liver involvement; its occurrence in 4 cases of severe chronic vomiting is not yet explained. The isolated increase of galactose in 10 of 12 cases was due to congenital galactosemia and only in 2 cases to other forms of liver disease.

For most diseases the number of cases studied is still too small to permit a final statement as to how frequently they are associated with mellituria. A preliminary attempt to give some information on this point is shown in Table VI. About one third of our patients with liver disease had mellituria, while in renal disease mellituria was essentially a feature of the nephrotic syndrome, where it occurred in two fifths of the cases. It is noteworthy that only 6 of 26 patients who on the basis of positive reduction tests were suspected of suffering from benign renal glucosuria did in fact excrete sugar in the urine. In Wilson's disease, as in some exogenous intoxications with heavy metals (e.g., lead), mellituria is a frequent but not obligatory sign of renal and hepatic damage. Nearly half the patients with inflammatory diseases of the gastrointestinal tract excreted increased amounts of sugar in the urine, mainly of lactose, though small increases of sucrose may also have been present but may have escaped detection.

*Comments.* A detailed discussion of the various forms of mellituria is not within the scope of this paper but has been published elsewhere.[1-7, 19] Here I will only comment on a few points of special interest. While renal familial glucosuria is generally considered to be a dominantly inherited disorder affecting only the glucose reabsorption and leaving the reabsorption of phosphates and amino acids intact,[28, 29] there is a heterogenous group of syndromes in which glucosuria is one of several manifestations of tubular dysfunction, the others being aminoaciduria, phosphaturia, polyuria, loss of fixed bases, and other disturbances of renal acid-base regulation. The patterns of these tubular syndromes vary from case to case in the several diseases. Though of multiform etiology many such syndromes have been published under the names of the 3 original authors as de Toni-Debré-Fanconi-syndrome; this has unfortunately led to undesirable generalizations and the confusion of different diseases.

The secondary and symptomatic form of this syndrome may be due to intoxication with lead,[18, 30, 31] copper (Wilson's disease),[32, 33] lysol,[34] uranium,[35] potassium ferric cyanide,[36] mercury,[37] sodium maleate,[38, 39] and other poisons. It has also been observed in the nephrotic syndrome, chronic nephritis, and acute tubular nephrosis,[18, 19, 24, 25, 40-42] in glycogen storage disease,[44] and in multiple myeloma.[45] In cystinosis the syndrome is usually present in a complete and fully developed form,[17] but even here we now tend to regard it as a secondary manifestation of a primary metabolic defect which slowly and progressively damages the renal tubule and indeed the whole kidney, leading to death in uremia. This view is in agreement with the observation that glucosuria, aminoaciduria, and other tubular signs develop slowly in the second half year of life[46] and may occasionally be absent even in fully developed cases. There remains a number of so-called idiopathic cases of the Fanconi syndrome in children and adults where the etiology is still quite obscure and where the presence of a congenital defect of tubular function and morphology[47, 48] has been discussed by various authors.[4, 49-51]

Table V. Disorders with isolated or generalized mellituria*

| | |
|---|---|
| Glucosuria (77 cases) | Diabetes mellitus, renal benign glucosuria, liver disease, tubular syndromes (de Toni-Debré-Fanconi syndrome, renal osteodystrophy, Lowe syndrome), tubular intoxication (hemoglobin, lead, vitamin D), nephrosis, nephritis, cystinosis, Wilson's disease, hypophyseal and adrenal dysfunctions |
| Lactosuria (13 cases) | Severe infantile gastroenteritis, steatorrhea, neonatal jaundice with septicemia, hiatus hernia |
| Fructosuria (12 cases) | Hepatitis and cirrhosis, Wilson's disease, hemoglobin intoxication, severe generalized infections, fructose intolerance |
| Galactosuria (12 cases) | Idiopathic galactosemia, severe liver damage, neonatal hepatitis |
| Excretion of lactose, galactose, glucose, and fructose (16 cases) | Acute infectious and toxic liver damage, toxic gastroenteritis, septicemia, severe rickets, pyloric stenosis, persistent vomiting |

*Only the diseases encountered in our 130 cases with mellitura are listed.

A variety of gastrointestinal disorders are associated with lactosuria and sucrosuria, which are probably the result of increased intestinal permeability and decreased activity of alpha glucosidase and lactase in the intestinal wall. Since v. Reuss'[10] description in 1910 many authors have observed this disaccharidiuria in infantile gastroenteritis[19, 52, 53]; it has also been found in sprue,[19, 54, 55] celiac disease,[19] and in hiatus hernia.[19, 26, 56, 57] The combination of hiatus hernia and disaccharidiuria with mental retardation (Moncrieff's syndrome)[26, 56, 57] has so far not been encountered by us; perhaps the disaccharidiuria of this syndrome is secondary to the hiatus hernia, which may lead to irritation and increased permeability of the gastric mucosa; there is no evidence of a causal relation between the disaccharidiuria and the brain damage. In young infants it may be difficult to distinguish between pathologic and physiologic lactosuria due to intestinal immaturity. "Idiopathic" lactosuria[58] and sucrosuria[59-61] have been described in very rare instances; in view of the negative reduction test the sucrosuria can easily be overlooked and may not be quite harmless, as high sucrose concentrations in blood and urine have been shown to produce irreversible renal damage of the type known as "osmotic nephrosis."[62]

While fructosuria, isolated or in combination with other melliturias, especially with galactosuria and glucosuria, is most frequently a sign of liver dysfunction, it may in rare instances be due to an inborn error of fructose metabolism. Essential benign fructosuria[63-71] has so far not been encountered by us. It is a recessively inherited harmless condition, which, like pentosuria, is occasionally diagnosed as diabetes because of the positive reduction test. The fructosuria of the recently described "hereditary fructose intolerance"[27, 72, 74] was in Wolf's case[27] very mild and may often be altogether absent because these patients quickly learn to abstain from foods containing fructose.

The diagnostic importance of detecting galactosuria in idiopathic galactosemia cannot be overrated and can only be compared with the demonstration of glucosuria in diabetes. While pronounced galactosuria is easily recognized by a positive reduction test in combination with a negative glucosidase

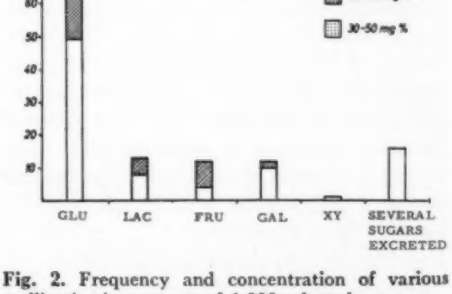



Fig. 2. Frequency and concentration of various melliturias in a group of 1,000 selected cases.

reaction (Clinitest, Glucotest), negative yeast fermentation, etc., the disease may escape detection in the acute phase, when infants refuse to take their formula, vomit, and excrete only small amounts of galactose of less than 100 mg. per 100 ml., showing a negative reduction test in the urine. At this stage the chromatographic demonstration of isolated galactosuria[16, 75] perhaps combined with aminoaciduria,[16, 76, 77] is of great importance in establishing the diagnosis. A galactose-free diet should then be started immediately, since otherwise many infants do not survive this stage of the disease. But it is also possible that in the mildest cases of galactosemia the galactose tolerance is only moderately reduced and that mere traces of galactose are excreted in the urine despite a milk intake up to 500 Gm. per day. A chronic intoxication by small amounts of galactose-1-phosphate may nevertheless produce mental deficiency in the long run. Here again the diagnosis can only be established by a sensitive method such as paper chromatography. In young infants the differential diagnosis between idiopathic galactosemia and other liver disorders such as hepatitis, atresia of the bile ducts, or familial cirrhosis may be difficult. In our experience isolated galactosuria is more common in galactosemia, while an absence of mellituria or a combined excretion of galactose, glucose, and fructose are the usual findings in the other liver diseases.

**Sugar loading tests.** There is no doubt that the excretion of sugar in the urine is considerably affected by the sugar intake. Most melliturias described earlier show up only if the sugars are ingested in sufficient amounts, and milder melliturias may be missed if the urine investigation is carried out in the fasting state. For these reasons we have attempted to establish a sugar loading test in which the 5 most important sugars were offered to the test subject as a "sugar cocktail" in about 500 ml. of weak tea, the urine being collected in the morning after overnight fasting and just before ingestion of sugar and then in three 60 minutes portions at 1, 2, and 3 hours after the ingestion.

**Table VI.** Some indications of the frequency of mellituria in various diseases

| *Clinical diagnosis* | *Mellituria* | |
|---|---|---|
| | *Present* | *Absent* |
| Liver diseases | 20 | 35 |
| including: Liver cirrhosis | 9 | 10 |
| Hepatitis | 7 | 19 |
| Kidney diseases | 12 | 40 |
| including: Nephrotic syndrome | 7 | 10 |
| Glomerulonephritis | 1 | 10 |
| Pyelonephritis | 2 | 15 |
| Interstitial nephritis | 1 | 3 |
| Renal benign glucosuria | 6 | 20 |
| Renal acidosis Lightwood | 1 | 14 |
| Cystinosis | 18 | 0 |
| Wilson's disease | 6 | 10 |
| Galactosemia | 9 | 0 |
| Gastroenteritis, enteritis | 8 | 10 |
| Rickets, resistant rickets | 2 | 48 |
| Scurvy | 0 | 4 |

**Table VII.** Composition of the "sugar cocktail."

| *Sugar* | *Sugar quantities in Gm.* | | |
|---|---|---|---|
| | *Toddlers (2 to 5 years)* | *School children (7 to 12 years)* | *Adults* |
| Glucose | 20 | 30 | 40 |
| Galactose | 4 | 6 | 8 |
| Fructose | 15 | 22.5 | 30 |
| Lactose | 4 | 6 | 8 |
| Sucrose | 10 | 15 | 20 |

At the outset it was necessary to determine the normal response to such sugar loads and to establish by trial and error the quantities of the various sugars which would generally produce a mild but still detectable mellituria in most healthy subjects. The sugar quantities needed for this purpose were considerably smaller than we had anticipated from a study of the literature; they are shown in Table VII. The test was performed on 20 healthy adults and 25 children, who received half or two thirds of the adult sugar dose in 200 to 400 ml. weak tea. The dose was adjusted according to the child's age. The results are given in Table VIII. All children and adults reacted to the sugar load with an increased excretion of at least one, more frequently of 3 or 4 sugars. The total excretion of these sugars in the 3 hours fol-

**Table VIII.** Average sugar excretion (M ± σ M) in the urine before and after sugar load

| | *Glucose (mg./hr.)* | *Galactose (mg./hr.)* | *Fructose (mg./hr.)* | *Lactose (mg./hr.)* | *Sucrose (mg./hr.)* |
|---|---|---|---|---|---|
| *20 healthy adults* | | | | | |
| Fasting | 1.2 ± 0.3 | 0.2 ± 0.1 | 0 | 0 | 0.1 ± 0.1 |
| First hour | 6.3 ± 2.0* | 8.2 ± 2.2* | 12.3 ± 2.8* | 0.5 ± 0.4 | 21.6 ± 7.3* |
| Second hour | 0.9 ± 0.4 | 3.0 ± 0.9 | 4.6 ± 1.6 | 1.3 ± 0.8 | 8.8 ± 2.9 |
| Third hour | 0 | 0.3 ± 0.2 | 0.1 ± 0.1 | 0.1 ± 0.1 | 4.1 ± 1.8 |
| *25 healthy children* | | | | | |
| Fasting | 0.1 ± 0.1 | 0.05 ± 0.03 | 0.1 ± 0.1 | 0 | 0.2 ± 0.1 |
| First hour | 1.4 ± 0.6† | 2.7 ± 0.8* | 4.1 ± 1.4* | 2.0 ± 0.9 | 4.6 ± 1.2* |
| Second hour | 0.3 ± 0.2 | 2.5 ± 0.7 | 2.8 ± 0.8 | 1.1 ± 0.9 | 9.0 ± 2.6 |
| Third hour | 0.3 ± 0.1 | 1.6 ± 0.6 | 1.5 ± 0.5 | 1.4 ± 0.8 | 5.2 ± 1.3 |

*Increase above the fasting value significant (level of significance < 2 per cent).

†Increase above the fasting value significant (level of significance < 5 per cent).

lowing the ingestion averaged for glucose 2.0 mg. in the children and 7.2 mg. in the adults; for galactose 6.8 and 11.5 mg., respectively, for fructose 8.4 and 17.0 mg., respectively, for lactose 4.5 and 1.9 mg., respectively, and for sucrose 18.8 and 34.5 mg., respectively. For glucose, galactose, fructose, and sucrose the increase above the fasting level was statistically significant; no significant increase was observed for lactose.

In order to rule out the possibility of any competitive action between the various ingested sugars at the site of intestinal absorption or of tubular reabsorption, the sugar excretion of one healthy adult was determined after ingestion of the cocktail and after ingestion of the single sugars. The results of these 2 sets of experiments were identical and no competition was observed.

The same sugar loading test was applied to patients suffering from disorders of the liver, the kidneys, and the intestinal tract. The results are reproduced in Tables IX to XI and may be summarized as follows.

1. Compared with the response of the normal controls, patients with hepatitis and cirrhosis of the liver showed an increase of the average excretion (M) of glucose, galactose, and fructose after the sugar load.

2. There was a marked increase of the average excretion of glucose in glomerulonephritis and to a lesser degree in pyelonephritis. Two cases of uremia and 2 cases of cystinosis exhibited strong glucosuria; the cystinoses also showed increased fructosuria.

3. The cases of gastroenteritis showed an increase in the average excretion of glucose and fructose, whereas in typhoid fever and dysentery only the excretion of glucose was raised. No definite increase above the normal response occurred in duodenal ulcer and ulcerative colitis.

In most instances the standard deviation (σ M) was too large to permit conclusions applicable to other specific cases. The large σ M is due to the varying severity of the disease, to the rather wide range of individual response, to the small number of cases, and to the technical errors involved in paper chromatography.

*Comments.* The results of the sugar loading tests are still very tentative, as this technique has only recently been used for the study of mellituria and has been applied to a limited case material. Perhaps the most interesting observation is the fact that mellituria can be elicited in the healthy child and adult by sugar doses well below those quoted by most workers in this field such as v. Noorden and Isaac,[78] Bürger,[79] and Breusch.[80] According to the first authors mild mellituria has been observed only after as much as 120 Gm. lactose, 150 to 200 Gm. sucrose, 120 to 150 Gm. fructose, more than 150 to 180 Gm. glucose, and 40 Gm. galactose; the other 2 authors

mention similar figures. Such quantities would make the application of a "sugar cocktail" impracticable. During our sugar loads mellituria was observed with quantities one-fifth or less than those of v. Noorden, which is probably at least partly due to our more sensitive technique. The lactose dose was too small for an optimal loading test and should in future be increased to 15 Gm. Even then the total sugar dose for adults contained in one sugar cocktail amounts to only 113 Gm., which is generally taken without difficulty. The children's dose has probably been reduced rather too much and might in future be increased to the adult dose in school children and to three-fourths of the adult dose in preschool children, though it may sometimes prove difficult to persuade very young children to take this amount.

Our results in cases of liver[18, 19, 81-89] and kidney[17-19, 24, 90-92] diseases agree with those of the previous section and with those in the literature. In many of our patients the mellituria was not present in the fasting state and was elicited only under the stress of the loading test. This indicates that the test provides one further possibility of appraising a functional disturbance of these organs.

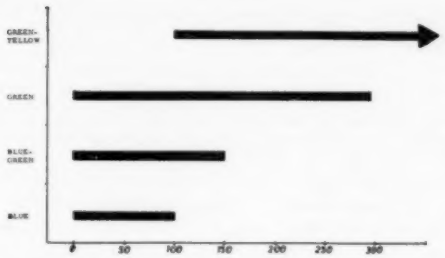



**Fig. 3.** Relation of the color reaction of Benedict's reduction test to the sugar concentration in 730 urines. The sugar concentration was determined by paper chromatography and expressed uniformly in glucose equivalents. Glucose concentrations of the urine expressed in milligrams per 100 ml.

The results in the group of patients with intestinal disorders were unrepresentative (Table XI), probably because the case material was unsuitable and the lactose load too small; this is also indicated by the low excretion figures and large standard deviation in the normal controls. The children were suffering from mild forms of gastroenteritis, typhoid fever, and dysentery, while in the adult group the cases of duodenal ulcer and ulcerative colitis were also mild and the disease was restricted to a limited part of the intestinal tract. Disaccharidurie occurred only sporadically, whereas gluco-

**Table IX.** Average sugar excretion (M ± σ M) in liver disease before and after sugar load

| | *Glucose (mg./hr.)* | *Galactose (mg./hr.)* | *Fructose (mg./hr.)* | *Lactose (mg./hr.)* | *Sucrose (mg./hr.)* |
|---|---|---|---|---|---|
| *12 adults with hepatitis* | | | | | |
| Fasting | 2.6 ± 0.7 | 0.4 ± 0.4 | 0.2 ± 0.2 | 0.6 ± 0.6 | 0 |
| First hour | 38.5 ± 17.3* | 20.0 ± 6.7† | 25.7 ± 7.8† | 0.3 ± 0.3 | 22.1 ± 7.5 |
| Second hour | 12.8 ± 7.2 | 10.7 ± 3.0 | 23.8 ± 8.9 | 3.7 ± 2.1 | 29.9 ± 9.8† |
| Third hour | 1.9 ± 0.7 | 6.5 ± 2.8 | 9.4 ± 4.6 | 2.0 ± 1.4 | 24.3 ± 8.6 |
| *6 adults with liver cirrhosis* | | | | | |
| Fasting | 3.8 ± 1.1 | 0 | 1.3 ± 0.9 | 0 | 1.7 ± 1.1 |
| First hour | 38.8 ± 36.2 | 22.7 ± 11.6 | 51.7 ± 30.5 | 0.7 ± 0.7 | 10.4 ± 7.7 |
| Second hour | 33.7 ± 24.3 | 44.2 ± 14.6* | 53.1 ± 24.2* | 1.3 ± 0.9 | 29.8 ± 9.1† |
| Third hour | 4.6 ± 1.8 | 6.7 ± 1.9 | 7.4 ± 3.1 | 1.9 ± 1.4 | 12.2 ± 4.9 |
| *3 children with hepatitis* | | | | | |
| Fasting | 0 | 0 | 0 | 0 | 0 |
| First hour | 0 | 4.5 ± 0.8† | 1.1 ± 1.1 | 0 | 4.6 ± 4.6 |
| Second hour | 0 | 9.6 ± 2.4 | 4.2 ± 2.1 | 0 | 8.7 ± 8.7 |
| Third hour | 0 | 2.8 ± 0.7 | 2.8 ± 1.7 | 0 | 7.6 ± 7.6 |

*Increase above the fasting value significant (level of significance < 5 per cent).

†Increase above the fasting value significant (level of significance < 2 per cent).

**Table X.** Average sugar excretion (M ± σ M) in kidney disease before and after sugar load

| | *Glucose (mg./hr.)* | *Galactose (mg./hr.)* | *Fructose (mg./hr.)* | *Lactose (mg./hr.)* | *Sucrose (mg./hr.)* |
|---|---|---|---|---|---|
| *8 adults and 5 children with glomerulonephritis* | | | | | |
| Fasting | 4.1 ± 2.0 | 0 | 0 | 0.9 ± 0.9 | 3.1 ± 2.1 |
| First hour | 14.6 ± 3.5* | 1.5 ± 1.0 | 2.3 ± 1.3 | 2.4 ± 2.4 | 15.6 ± 11.8 |
| Second hour | 6.7 ± 2.2 | 2.1 ± 0.8* | 4.8 ± 1.9* | 7.5 ± 3.3 | 29.3 ± 17.5 |
| Third hour | 3.3 ± 1.2 | 1.2 ± 0.5 | 3.6 ± 1.4 | 6.4 ± 3.2 | 27.3 ± 16.5 |
| *5 adults and 4 children with pyelonephritis* | | | | | |
| Fasting | 1.5 ± 0.9 | 0.1 ± 0.1 | 0 | 1.5 ± 1.5 | 0 |
| First hour | 8.9 ± 7.4 | 0.9 ± 0.9 | 6.2 ± 4.8 | 0 | 7.9 ± 5.4 |
| Second hour | 2.3 ± 1.0 | 1.3 ± 0.4* | 3.7 ± 1.2* | 2.1 ± 0.6 | 8.3 ± 2.3* |
| Third hour | 1.5 ± 0.7 | 0.2 ± 0.2 | 1.9 ± 0.8 | 1.2 ± 0.3 | 0 |
| *2 adults with uremia* | | | | | |
| Fasting | 20.0 | 0 | 0 | 0 | 0 |
| First hour | 58.0 | 0 | 2.3 | 0 | 0 |
| Second hour | 134.7 | 0 | 2.3 | 0 | 0 |
| Third hour | 50.1 | 0 | 2.8 | 0 | 0 |
| *2 children with cystinosis* | | | | | |
| Fasting | 17.5 | 0 | 0 | 0 | 0 |
| First hour | 402.0 | 0 | 22.8 | 0 | 0 |
| Second hour | 412.0 | 0 | 19.1 | 0 | 0 |
| Third hour | 72.5 | 0 | 9.1 | 0 | 0 |

*Increase above the fasting value significant (level of significance < 2 per cent).

**Table XI.** Average sugar excretion (M ± σ M) in diseases of the digestive tract, before and after sugar load

| | *Glucose (mg./hr.)* | *Galactose (mg./hr.)* | *Fructose (mg./hr.)* | *Lactose (mg./hr.)* | *Sucrose (mg./hr.)* |
|---|---|---|---|---|---|
| *6 children with gastroenteritis* | | | | | |
| Fasting | 0.9 ± 0.3 | 0.2 ± 0.2 | 1.5 ± 0.8 | 0 | 0 |
| First hour | 8.5 ± 2.1* | 0.7 ± 0.7 | 6.7 ± 1.0* | 2.2 ± 2.2 | 5.8 ± 5.5 |
| Second hour | 8.6 ± 2.5 | 0.7 ± 0.4 | 8.2 ± 2.9 | 2.8 ± 1.4 | 1.3 ± 0.6† |
| Third hour | 10.1 ± 4.5 | 0 | 8.8 ± 4.3 | 9.6 ± 7.4 | 3.0 ± 1.6 |
| *4 children with typhoid fever and dysentery* | | | | | |
| Fasting | 0.8 ± 0.1 | 0 | 0.2 ± 0.2 | 0 | 0 |
| First hour | 19.9 ± 17.0 | 1.8 ± 1.2 | 3.5 ± 1.3* | 0 | 14.3 ± 8.2 |
| Second hour | 4.4 ± 1.1* | 2.0 ± 2.0 | 1.6 ± 1.3 | 0 | 14.0 ± 11.5 |
| Third hour | 1.5 ± 1.2 | 0 | 0.2 ± 0.2 | 0.4 ± 0.4 | 8.2 ± 6.8 |
| *4 adults with duodenal ulcer* | | | | | |
| Fasting | 2.3 ± 1.0 | 0 | 0 | 0 | 0 |
| First hour | 7.1 ± 3.9 | 6.1 ± 2.3* | 4.6 ± 3.6 | 0 | 11.6 ± 6.7 |
| Second hour | 4.5 ± 1.8 | 2.2 ± 1.3 | 1.9 ± 1.2 | 0 | 15.2 ± 10.2 |
| Third hour | 0.9 ± 0.2 | 0.5 ± 0.5 | 0.5 ± 0.5 | 0 | 8.8 ± 7.8 |
| *4 adults with ulcerative colitis* | | | | | |
| Fasting | 2.9 ± 1.1 | 0 | 0 | 0 | 0 |
| First hour | 10.9 ± 5.3 | 2.6 ± 2.2 | 4.4 ± 2.2 | 2.0 ± 2.0 | 7.8 ± 7.8 |
| Second hour | 6.3 ± 1.8 | 2.4 ± 1.9 | 5.1 ± 4.5 | 6.9 ± 6.9 | 17.3 ± 17.3 |
| Third hour | 2.6 ± 0.7 | 1.1 ± 1.1 | 2.5 ± 1.0 | 5.5 ± 5.5 | 14.5 ± 14.5 |

*Increase above the fasting value significant (level of significance < 2 per cent).

†Increase above the fasting value significant (level of significance < 5 per cent).

suria and fructosuria were seen more frequently. The sugar pattern to be expected in severe involvement of the intestinal tract has been discussed in the previous section.

**Comparison of the chromatographic results with those of Benedict's test.** 730 urines collected during the sugar loading tests were used for this comparison, Benedict's reduction test being carried out as described above. The quantity of the various sugars was determined chromatographically and their total reduction power was expressed uniformly according to Bertrand's tables[23] as the glucose equivalent of the same reduction power. The figures given for the glucose concentrations in the next paragraph thus stand for glucose equivalents, not for true glucose.

Fig. 3 summarizes the results, and some further data may be added. Twenty-seven of 590 urines with blue color reactions contained more than 50 mg. glucose (up to 104 mg.) per 100 ml.; 8 of 46 urines with blue-green color reactions contained more than 80 mg. glucose (up to 156 mg.) per 100 ml. A green color reaction was noticed in 79 specimens, 22 of which showed glucose concentrations above 150, and up to 290 mg. per 100 ml. Of 15 specimens with a green-yellow color reaction all exhibited mellituria with glucose concentrations between 115 and 550 mg. per 100 ml. On the other hand, 14 of the 79 specimens with a green color reaction showed glucose concentrations below 50 mg. per 100 ml.

These results agree fairly well with earlier studies by Bickel[19] and Apthorp,[24] though the last author evaluated the Benedict test somewhat differently by the color of the precipitate in the unshaken test tube. Our findings underline the fact that the universally used reduction tests are not only unspecific but also too insensitive for careful clinical investigations. It has been shown that for most sugars concentrations above 20 to 30 mg. per 100 ml. are pathologic, but concentrations up to 150 mg. per 100 ml. may still be associated with a negative (blue or blue-green) Benedict reaction. Clinically important melliturias (e.g., galactosuria) can thus be overlooked, while a green color reaction may not be due to sugar at all but to other reducing substances in the urine. We are forced to conclude that the traditional reduction test, though useful for detecting severe melliturias with sugar concentrations above 150 mg. per 100 ml., is of little value in the melliturias with milder sugar excretion.

## SUMMARY

The study of various forms of mellituria has been neglected by the clinician for technical reasons. One-dimensional paper chromatography is a suitable new technique for extending our knowledge of this subject, as it is both sensitive and specific and can be performed in any clinical laboratory. The method we have used for the last 8 years is described in some detail.

The sugar excretion in 170 twenty-four–hour urine collections of 104 full-term and premature infants has been examined and a physiologic mellituria has been observed with a moderate increase of glucose, galactose, fructose, and lactose, which lasts for the first 10 to 14 days. The pattern of the mellituria points to immature functions of the renal tubule, the liver, and the intestinal tract. There is no close time relation to the physiologic aminoaciduria of infancy. In 125 healthy children and adults, urinary excretion of sugar was minimal or absent.

To obtain a general idea of the urinary sugar pattern in various diseases 1,000 selected patients were investigated, 130 of whom showed mellituria. In 114 instances the mellituria was due to the increase of a single sugar, namely to glucose in 77 cases, lactose in 13, fructose in 12, galactose in 11, and xyloketose in 1, respectively. In 16 cases the mellituria was due to an increase of more than one sugar. The diseases associated with these melliturias are discussed and some tentative figures are given as to the frequency of this association. Isolated and constant melliturias are characteristic of inborn errors of sugar metabolism while symptomatic melliturias are more variable in pattern and occurrence, though different sugar patterns

can be distinguished in hepatic, renal, and intestinal disorders.

The sugar excretion in the urine is affected by the sugar intake. To establish standard test conditions a sugar loading test was devised by mixing 40 Gm. glucose, 8 Gm. galactose, 30 Gm. fructose, 8 Gm. lactose, and 20 Gm. sucrose into a sugar "cocktail." This amount was given to adults and two-thirds or one-half of it to children. Urine was collected in the fasting state and at 1, 2, and 3 hours after the sugar load. Although mild mellituria occurred after the load in every one of 45 healthy controls, the sugar increase was more pronounced in diseases of the liver, kidney, and intestine. The diagnostic possibilities of such a loading test are underlined by the fact that the fasting urine repeatedly failed to show mellituria.

There was a poor correlation between the chromatographic results and Benedict's reduction test. Sugar concentrations up to 150 mg. per 100 ml. were associated with blue or blue-green Benedict reactions, and green reactions repeatedly occurred in urines free from sugar. Definite and diagnostically important melliturias such as idiopathic galactosuria may be missed if clinical investigations are limited to reduction tests, even as a screening procedure. For the accurate diagnosis of mellituria, paper chromatography is recommended as a routine procedure.

## REFERENCES


1. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Interpretations, vol. 1, London, 1946, Baillière, Tyndall & Cox, pp. 189, 334, 342.
2. Joslin, E. P., Root, H. F., White, P., and Marble, A.: The Treatment of Diabetes Mellitus, Philadelphia, 1946 and 1952, Lea & Febiger.
3. Bernheim, M., François, R., and Ruitton-Ugliengo: Les mélituries non diabetiques chez l'enfant, Rapport au XVome Congrès des Pédiatres de Langue française, Marseille, 1955, Sopic.
4. Royer, P., and Prader, A.: Les insuffisances congénitales du tubule rénal chez l'enfant. Clinique et therapeutique. 16e congrès des pédiatres de langue française, Paris, 1957, L'expansion scientifique française, p. 308.
5. Chaptal, J., and Jean, R.: Le diabète rénal, L'Hôpital **46:** 222, 1958.
6. Schreier, K.: Die nichtdiabetischen Melliturien, Ergebn. inn. Med. u. Kinderh. **12:** 493, 1959.
7. Bickel, H.: Die nicht-diabetischen Melliturien des Kindes, Mod. probl. paediat. **6:** 313, 1960.
8. Hoeniger, E.: Über die ephemere traumatische Glykosurie bei Neugeborenen, Deutsche med. Wchnschr., 1911, p. 500.
9. Nothmann, H.: Beitrag zur Zuckerausscheidung im Säuglingsalter, Ztschr. Kinderh. **2:** 503, 1911.
10. v. Reuss, A.: Über alimentäre Saccharosurie bei darmkranken Säuglingen, Wien. klin. Wchnschr. **23:** 123, 1910.
11. Rietschel, H.: Inanition u. Zuckerausscheidung im Säuglingsalter, Ztschr. Kinderh. **7:** 282, 1913.
12. Mayerhofen, E.: Der Harn des Säuglings, Ergebn. inn. Med. u. Kinderh. **12:** 553, 1913.
13. Lasker, M.: The Question of Arabinosuria With a Scheme for Identifying Reducing Substances in Urine, Am. J. Clin. Path. **20:** 485, 1950.
14. Partridge, S. M., and Westall, R. G.: Filter-Paper-Partition Chromatography of Sugars, Biochem. J. **42:** 238, 1948.
15. Horrocks, R. H., and Manning, G. B.: Partition Chromatography on Paper. Identification of Reducing Substances in Urine, Lancet **1:** 1042, 1949.
16. Bickel, H., and Hickmans, E. M.: Paper Chromatograpihc Investigations of the Urine of Patients With Galactosaemia (Appendix), Arch. Dis. Childhood **27:** 348, 1952.
17. Bickel, H., Baar, H. S., Astley, R., Douglas, A. A., Finch, E., Harris, H., Harvey, C. C., Hickmans, E. M., Philpot, M. G., Smallwood, W. C., Smellie, J. M., and Teall, C. G.: Cystine Storage Disease With Aminoaciduria and Dwarfism (Lignac-Fanconi Disease), Acta paediat. **42:** 1, suppl. 90, 1952.
18. Bickel, H., and Souchon, F.: Die Papierchromatographie in der Kinderheilkunde, Arch. Kinderh., suppl. 31, 1955.
19. Bickel, H.: Zur klinischen Bedeutung verschiedener Melliturien, Mod. probl. paediat. **4:** 136, 1959.
20. Bickel, H.: Die Aminosäuren- und Zuckerrückresorption im Tubulus reifer und frühgeborener Kinder, in: Linneweh, F.: Die physiologische Entwicklung des Kindes, Heidelberg, 1959, Springer-Verlag, p. 240.
21. Woolf, L. I.: Use of Ion-Exchange Resins in Paper Chromatography of Sugars, Nature **171:** 841, 1953.

22a. Haworth, J. C., and McCredie, D.: Chromatographic Separation of Reducing Sugars in the Urine of Newborn Babies, Arch. Dis. Childhood **31:** 189, 1956.

22b. Haworth, J. C., and MacDonald, M. S.: Reducing Sugars in the Urine and Blood of

Premature Babies, Arch. Dis. Childhood **32:** 417, 1957.
23. Woolf, L. I., and Norman, A. P.: The Urinary Excretion of Amino Acids and Sugars in Early Infancy, J. PEDIAT. **50:** 271, 1957.
24. Apthorp, G. H.: Investigation of the Sugar Content of Urine From Normal Subjects and Patients With Renal and Hepatic Disease by Paper Chromatography, J. Clin. Path. **10:** 84, 1957.
25. Lowe, K. G., Moodie, G., and Thomson, M. B.: Glycosuria in Acute Tubular Necrosis, Clin. Sc. **13:** 187, 1954.
26. Moncrieff, A., and Wilkinson, R. H.: Sucrosuria With Mental Defect and Hiatus Hernia, Acta paediat. **43:** 495, suppl. 100, 1954.
27. Wolf, H., Zschocke, D., Wedemeyer, F. W., and Hübner, W.: Angeborene hereditäre Fructoseintoleranz, Klin. Wchnschr. **37:** 693, 1959.
28. Chisolm, J. J., Jr., Harrison, H. E., and Zitiert von Mudge, G. H.: Clinical Patterns of Tubular Dysfunction, Am. J. Med. **24:** 785, 1958.
29. Govaerts, P., and Lambert, P. P.: Pathogénie du diabète rénal, Acta clin. belg. **4:** 1, 1949.
30. Chisolm, J. J., Harrison, H. C., Eberlein, W. R., and Harrison, H. E.: Amino-aciduria, Hypophosphatemia and Rickets in Lead Poisoning, Am. J. Dis. Childhood **89:** 159, 1955.
31. Wilson, V. K., Thomson, M. L., and Dent, C. E.: Aminoaciduria in Lead Poisoning, A Case in Childhood, Lancet **2:** 66, 1953.
32. Bickel, H.: Neuere Erkenntnisse zur hepatocerebralen Degeneration (Wilson'sche Krankheit), Mod. probl. paediat. **3:** 215, 1957.
33. Bickel, H.: Störungen der Aminosäuren- und Zuckerrückresorption im proximalen Tubulus. Einige physiologische und klinische Gesichtspunkte, Monatsschr. Kinderh. **106:** 162, 1958.
34. Spencer, A. G., and Franglen, G. T.: Gross Aminoaciduria Following a Lysol Burn, Lancet **1:** 190, 1952.
35. Wilson, V. K., Thomson, M. L., and Dent, C. E.: in Voegtlin, C., and Hodge, H. C., editors: Pharmacology and Toxicology of Uranium Compounds, New York, 1949, McGraw-Hill Book Company, Inc.
36. Reubi, F.: Die tubulären Nierensyndrome, Ergebn. inn. Med. Kinderh. **9:** 154, 1958.
37. Kaplan, S. A., and Fomon, S. J.: Function Recovery Pattern in Acute Renal Failure Following Ingestion of Mercuric Chloride, Am. J. Dis. Childhood **85:** 633, 1953.
38. Harrison, H. E., and Harrison, H. C.: Experimental Production of Renal Glycosuria, Phosphaturia and Aminoaciduria by Injection of Maleic Acid, Science **120:** 606, 1954.
39. Durand, P., Manzini, W., Bruni, R., and Semach, F.: Ricerhe sperimentali sulla mellituria, iperfosfaturia, iperaminoaciduria da somministratione di acido maleico, Minerva pediat. **8:** 1073, 1956.
40. Hawkins, J. A., MacKay, E. M., and Van Slyke, D. D.: Glucose Excretion in Bright's Disease, J. Clin. Invest. **8:** 107, 1929.
41. Tegelaers, W. H. H., and Tiddens, H. W.: Nephrotic-Glucosuric Amino-Aciduric Dwarfism and Electrolyte Metabolism, Helvet. paediat. acta. **10:** 269, 1955.
42. Woolf, L. I., and Giles, H. McC.: Urinary Excretion of Amino-Acids and Sugar in the Nephrotic Syndrome. A Chromatographic Study, Acta paediat. **45:** 489, 1956.
43. Hooft, C., and Herpol, J.: Aminoaciduria in the Course of Lipoid Nephrosis in Children. The Influence of ACTH, Acta paediat. **48:** 135, 1959.
44. Fanconi, G., and Bickel, H.: Die chronische Aminoacidurie (Amino-säurediabetes oder nephrotisch-glukosurischer Zwergwuchs) bei der Glykogenose und der Cystinkrankheit, Helvet. paediat. acta **4:** 359, 1949.
45. Engle, R. L., Jr., and Wallis, L. A.: Multiple Myeloma and the Adult Fanconi Syndrome. I. Report of Case With Crystal-like Deposits in Tumor Cells and in Epithelial Cells of the Kidney, Am. J. Med. **22:** 5, 1957.
46. Bickel, H.: Die Entwicklung der biochemischen Läsion bei der Lignac-Fanconischen Krankheit, Helvet. paediat. acta **10:** 259, 1955.
47. Clay, R. D., Darmady, E. M., and Hawkins, M.: The Nature of the Renal Lesion in the Fanconi syndrome, J. Path. **65:** 551, 1953.
48. Darmady, E. M., and Stranack, F.: Microdissection of the Nephron in Disease, Brit. M. Bull. **13:** 21, 1957.
49. Dent, C. E., and Harris, H.: Hereditary Forms of Rickets and Osteomalacia, J. Bone & Joint Surg. **38B:** 204, 1956.
50. Wallis, L. A., and Engle, R. L.: The Adult Fanconi Syndrome. Review of 18 Cases, Am. J. Med. **21:** 13, 1956.
51. Kuhlencordt, F.: Die glucosurische Osteopathie (Das sog. Fanconi-Syndrom beim Erwachsenen), Ergebn. inn. Med. Kinderh. **9:** 622, 1958.
52. Woringer, P.: La saccharosurie dans le choléra infantile, Arch. de méd. d. enf. **25:** 129, 1922.
53. Owen, J. A., and Lewis, I. C.: Sucrosuria in Children, Scot. M. J. **1:** 231, 1956.
54. Santini, R., Jr., Perez-Santiago, E., Martinez-de Jesus, J., and Butterworth, C. E., Jr.: Evidence of Increased Intestinal Absorption of Molecular Sucrose in Sprue, Am. J. Digest. Dis. **2:** 663, 1957.
55. Santini, R., Jr., Aviles, J., and Sheehy, T. W.: Sucrase Activity in the Intestinal Mucosa of Patients With Sprue and Normal Subjects, Am. J. Digest. Dis. **5:** 1059, 1960.
56. Heijkenskjöld, F., and Winberg, J.: Moncrieff's Syndrome–Hiatus Hernia, Mental Deficiency and Sucrosuria, Acta paediat. **46:** 409, 1957.
57. Woodruff, G. G.: Sucrosuria in Association With Mental Deficiency and Hiatal Hernia, J. PEDIAT. **52:** 66, 1958.
58. Durand, P.: Lattosuria idiopatica in una paziente con diarrea cronica ed acidosi, Minerva pediat. **10:** 706, 1958.

59. Elmer, A. W., Krasowska, M., and Ptaszek, L.: Sucrosuria. A Rare Metabolic Error, Acta med. Scandinav. **101:** 596, 1939.
60. Miriam, R., and Weiner, S. B.: Saccharosuria in an Infant, Am. J. Dis. Childhood **59:** 590, 1939.
61. Reiner, M., and Weiner, S. B.: Saccharosuria in an Infant, Am. J. Dis. Childhood **57:** 590, 1939.
62. Parmentier, R., and Corvilain, J.: Sur les lésions nephrotiques provoquées par le sucrose, Rev. belge path. et méd. exper. **25:** 210, 1956.
63. Anschel, N.: Untersuchungen über den Zuckerstoffwechsel an einem Fall von spontaner Lävulosurie, Klin. Wchnschr. **9:** 1400, 1930.
64. Marble, A., and Smith, R. M.: Essential Fructosuria, J. A. M. A. **106:** 24, 1936.
65. Oster, K.: Blutzuckeruntersuchungen in einem Fall von Lävulosurie, Monatsschr. Kinderh. **67:** 155, 1936.
66. Edhem, E. F., Erden, F., and Steinitz, K.: Etudes sur. un cas de lévolusurie essentielle, Acta med. scandinav. **97:** 455, 1938.
67. Lasker, M.: Essential Fructosuria, Human Biol. **13:** 51, 1941.
68. Linneweh, F.: Über den intermediären Kohlehydratstoffwechsel. Untersuchungen bei Lävulosurie, Klin. Wchnschr. **20:** 1020, 1941.
69. Ölgen, T.: Three Cases of Essential Fructosuria, Istanbul Contributions, Clin. Sc. **2:** 286, 1953.
70. Lenzner, A. R.: Fructosuria: Report of a Case, Ann. Int. Med. **45:** 702, 1956.
71. Cantoni, M., and Klinger, R.: Sulla levulosuria essenziale infantile. A proposito di un caso clinico, Minerva med. **48:** 1092, 1957.
72. Chambers, R. A., and Pratt, R. T.: Idiosyncrasy to Fructose, Lancet **2:** 340, 1956.
73. Froesch, E. R., Prader, A., Labhart, A., Stuber, H. W., and Wolf, H. P.: Die hereditäre Fructoseintoleranz, eine bisher nicht bekannte kongenitale Stoffwechselstörung, Schweiz. med. Wchnschr. **87:** 1168, 1957.
74. Froesch, E. R., Prader, A., Wolf, H. P., and Labhart, A.: Die hereditäre Fruktoseintoleranz, Helvet. paediat. acta **14:** 99, 1959.
75. Lockhart, J. D., and Roboz, E.: Case of Galactosemia Identified in a Four Day Old Infant by Paper Chromatographic Technique, Pediatrics **13:** 211, 1954.
76. Holzel, A., Komrower, G. M., and Wilson, V. K.: Aminoaciduria in Galactosaemia, Brit. M. J. **1:** 194, 1952.
77. Hsia, D. Y. Y., Hsia, H., Green, S., Kay, M., and Gellis, S. S.: Aminoaciduria in Galactosemia, A. M. A. Am. J. Dis. Childhood **88:** 458, 1954.
78. v. Noorden and Isaac, S.: Die Zuckerkrankheit, Berlin, 1928, p. 42.
79. Bürger, M.: Einführung in die Pathologische Physiologie, Leipzig, 1949, George Thieme Verlag, p. 316.
80. Breusch, F. L.: Biologen und Chemiker, in Flaschenträger, B., and Lehnartz, E.: Physiologische Chemie. Ein Lehr- und Handbuch für Ärzte, ed. 2, Berlin, 1954, Springer-Verlag, p. 734.
81. Mertz, A., and Rominger, E.: Experimentelle Blutzuckeruntersuchungen bei Kindern., Arch. f. Kinderh. **69:** 81, 1921.
82. Knauer, H., and Friedländer, K.: Stoffwechseluntersuchungen bei kindlicher Lebercirrhose, Jahrb. f. Kinderh. **120:** 292, 1928.
83. Stewart, C. P., Scarborough, H., Davidson, J. N.: Some Observations on the Laevulose Tolerance Test, Quart. J. Med. **7:** 229, 1938.
84. Köhler, V.: Einfluss des synthetischen Nebennierenrindenhormons auf die Lävuloseprobe bei Lebercirrhose. Klin. Wchnschr. **2:** 716, 1947.
85. Schneiderbaur, A.: Der Einfluss von Lävulose und Dextrose auf die alimentäre Galaktosurie bei Leberparenchymerkrankungen, Wien. klin. Wchnschr., 1950, p. 132.
86. Wallenfels, K.: Über das Vorkommen von freier Fruktose im menschlichen Blut, Naturwissenschaften **38:** 238, 1951.
87. Trautwein, H., and Grünefeld, H.: Die Verwertung intraduodenal zugeführten Zuckers (Dextrose- und Honigl ösung) bei Gesunden und bei Leberkranken, Arzneimittel Forsch. **7:** I/503, 1953.
88. Smith, L. H., Jr., Ettinger, R. H., Seligson, D., and Lightcap, S.: A Comparison of the Metabolism of Fructose and Glucose in Hepatic Disease and Diabetes Mellitus, J. Clin. Invest. **32:** 272, 1953.
89. Jorde, W. O.: Beitrag zum Laevulose- und Kreatinstoffwechsel, Ztschr. ges. Exper. Med. **121:** 170, 1953.
90. MacKay, R. L.: Observations on the Renal Threshold for Glucose, Biochem. J. **21:** 760, 1927.
91. Hawkins, J. A., MacKay, E. M., and Van Slyke, D. D.: Glucose in the Urine of Normal and Nephritic Subjects, J. Biol. Chem. **78:** 23, 1928.
92. Hawkins, J. A., MacKay, E. M., and Van Slyke, D. D.: Glucose Excretion in Bright's Disease, J. Clin. Invest. **8:** 107, 1929.
93. Bertrand, G.: Le dosage des sucres réducteurs, Bull. Soc. chim. biol. **35:** 1285, 1906.

# Congenital abnormalities of the urinary system

## II. Renal cortical and medullary necrosis

**Jay Bernstein, M.D.,* and Ruben Meyer, M.D.**

DETROIT, MICH.

RENAL cortical necrosis is relatively uncommon in infancy, and it has been only rarely described in newborn infants. As part of a general survey of congenital abnormalities of the kidneys and lower urinary tract,[1] our attention has been directed to those cases of renal cortical and medullary necrosis which occurred in the first week of life, when such lesions might be regarded as having been present from birth. These lesions have been observed in both their initial and relatively late stages, the latter providing some information on reparative processes during the perinatal period.

Some cases of "hemorrhagic nephritis" described in the older literature may have been examples of cortical necrosis,[2] and the studies of Campbell and Henderson[3] in 1949 and of Zuelzer and associates[4] in 1951 have drawn attention to this condition in the pediatric age group. The latter study included, among 11 cases of symmetrical renal cortical necrosis, 3 that occurred in the first week of life. One baby had mesenteric arterial thrombosis with diarrhea and intestinal gangrene, the second had had anemic shock because of erythroblastosis fetalis, and the third had had asphyxia neonatorum. Bland, ischemic necrosis with variable hemorrhage involved all structural elements in the renal cortices of the first 2 cases; the necrosis was limited to the tubular epithelium in the third, which was regarded as having had an "early" lesion. Another case of cortical necrosis, recently reported by Eskeland and Skogrand,[5] was that of a premature infant who died at the age of 2½ days, following repair of a tracheo-esophageal fistula. He also had adrenal hypoplasia; there was no anatomic evidence of infection. None of these infants had demonstrable intrarenal thrombi.

Medullary necrosis has also been described in newborn infants, generally occurring in association with hyperbilirubinemia and kernicterus.[6, 7] These lesions, in this situation, probably correspond to the bilirubin infarcts[8] and focal papillary necrosis[9, 10] seen in icterus gravis of the newborn. In a case recently reported by Marks,[11] renal medullary necrosis was observed in a newborn infant who appeared to have been exsanguinated by hemorrhage from the umbilical cord. Each medulla was entirely involved by ischemic necrosis; the cortices were spared, aside from some tubular necrosis at the

*From the Departments of Pathology and Pediatrics, Children's Hospital of Michigan, and Wayne State University College of Medicine, Detroit, Michigan.*

**Address, Children's Hospital of Michigan, 5224 St. Antoine Street, Detroit, 2, Mich.*

**Table I.** Clinical observations

| *Case No.* | *Race and sex* | *Birth weight (pound, ounce)* | *Body length (cm.)* | *Complications of pregnancy* | *Physical findings* |
|---|---|---|---|---|---|
| 1 | W<br>F | --- | 46 | Uterine and/or placental hemorrhage at delivery<br>"Abnormal vascular insertion" in placenta | Pallor<br>Lethargy and flaccidity<br>Dyspnea |
| 2 | W<br>M | --- | 52 | Polyhydramnios | Cyanosis<br>Lethargy<br>Dyspnea |
| 3 | W<br>M | 2,10 | 39 | Placenta previa | Dyspnea and apnea<br>Slight jaundice |
| 4 | N<br>F | 6,12 | 49 | Fetal bradycardia<br>Meconium-stained amniotic fluid<br>Postnatal apnea, 30 min. | Cyanosis<br>Dyspnea<br>Bleeding from mouth and nose<br>Cutaneous petechiae<br>Pulmonary râles |
| 5 | N<br>F | 5,5 | 45 | Eclampsia and cesarean section | Cyanosis<br>Lethargy and flaccidity<br>Poor reflexes<br>Dyspnea and apnea<br>Pulmonary râles |
| 6 | N<br>F | 6,7 | 50 | Pre-eclampsia<br>Second of twins; breech, midforceps<br>Postnatal apnea, 25 min. | Cyanosis<br>Poor reflexes<br>Dyspnea and apnea<br>Convulsions<br>Abdominal distention and pneumoperitoneum |
| 7 | N<br>M | 8,9 | 59 | Pre-eclampsia<br>Premature rupture of membranes | Pallor and cyanosis<br>Poor reflexes<br>Weak heart sounds<br>Cutaneous petechiae<br>Long fingernails and cutaneous desquamation |
| 8 | N<br>F | --- | 47 | Second of twins<br>Version and extraction<br>Bleeding from cord<br>Pallid placenta | Pallor and cyanosis<br>Flaccidity<br>Absent reflexes<br>Hypopnea |
| 9 | W<br>M | --- | 48.5 | Spontaneous premature labor following auto accident<br>Postnatal apnea, 30 min. | Pallor and cyanosis<br>Hypopnea |
| 10 | W<br>F | 5,11 | 48 | Slight vaginal bleeding | Cyanosis (3rd day)<br>Lethargy<br>Absent reflexes<br>Dyspnea<br>Slight jaundice |
| 11 | W | 6,8 | 49.5 | Cesarean section for prolonged labor and face presentation<br>Polyhydramnios | Poor reflexes<br>Dyspnea and pulmonary râles<br>Cutaneous petechiae<br>Febricula |

| Blood | | Urine | | Course and treatment | Age at death |
|---|---|---|---|---|---|
| Hemoglobin (Gm./100 ml.) | Nucleated red blood cell/100 white blood cell | Anuria | Hematuria | | |
| 7 | -- | Possible | - | Shock<br>Transfused with sedimented erythrocytes<br>Exchange transfusion started | 7 hours |
| 11.5 | 12 | Possible | - | Right diaphragmatic hernia repaired at 8 hours; transfused<br>Generalized postoperative hemorrhage following accidental heparinization<br>Hemoglobin down to 8.5 Gm./100 ml.; transfused | 31 hours |
| 14.5 | 27 | 0 | - | Continuing respiratory distress<br>Progressive abdominal distention | 7½ days |
| 20 | 53 | Terminal | + | Jaundice<br>Gastrointestinal hemorrhage; thrombocytopenia<br>Roentgenographic pulmonary opacification<br>Continuing severe respiratory distress | 26 hours |
| 17 | 22 | 0 | + | Abdominal distention<br>Continuing lethargy and respiratory distress | 4 days |
| 18.5 | 0 | + | - | Gastric perforation repaired<br>Recurring apnea | 2 days |
| 11 | 4 | + | - | Moderate anemia due to A-O isoimmunization<br>Hemoglobin falling to 9 Gm./100 ml.; transfused<br>Respiratory distress at 10 hours; apnea | 39 hours |
| 11.6 | 36 | + | - | Transfused with sedimented erythrocytes<br>Continuing flaccidity and unresponsiveness<br>Respiratory distress and apnea | 32 hours |
| 15 | -- | 0 | + | Flaccidity and apnea | 15 hours |
| 12 | 78 | 0 | + | Congestive heart failure with hepatomegaly<br>Intestinal bleeding; transfused<br>Progressive respiratory distress | 4 days |
| 13.3 | 25 | 0 | + | Bacteremia *(E. coli)*<br>Progressive hypopnea | 36 hours |

corticomedullary junctions, and thrombi were not encountered. Marks suggested that renal ischemia due to hypotension and vasospasm was responsible for the lesion.

The case material for this report includes 4 infants who were previously mentioned in the general survey of congenital renal abnormalities[1] and 7 observed subsequently. These were encountered during a 5-year period (1956 to 1960) in a series of 1,094 autopsies, of which approximately one third were performed on newborn infants.

## CLINICAL MATERIAL

The cases which comprise this report (Table I) are evenly divided between male and female and between white and Negro. Only 3 of the 11 infants were premature, as determined by body lengths of less than 47 cm.; one other infant did measure 47 cm., and the remaining 7 measured 48 cm. or more. One infant measured 59 cm. and was probably postmature.

Only Cases 3, 7, and 10 were not abnormal at birth. In the others, varying degrees of lethargy and respiratory difficulty were present immediately after delivery. Case 2 had a congenital diaphragmatic hernia, which undoubtedly contributed to his difficulty, and Case 6 suffered a spontaneous gastric perforation.

Three infants (Cases 4, 5, and 6) suffered from intrauterine asphyxia, and apnea was present for approximately a half hour after delivery in Cases 4 and 6. Postnatal asphyxia was also present in Case 9, when the infant was apneic for a similar period of time.

Factors promoting intrauterine asphyxia included preeclampsia (Cases 6 and 7), eclampsia (Case 5), and placenta previa (Cases 5 and 11). Polyhydramnios was present in 2 pregnancies; in Case 2 it may have been related to high intestinal obstruction because of a right-sided diaphragmatic hernia, but no predisposing factors were observed in Case 11. Uterine or utero-placental hemorrhage was observed in Cases 1, 3, 8, and 10, and it may have contributed to intrauterine anoxia.

The observed utero-placental hemorrhage was, however, associated with anemia in these infants. Cases 1 and 8 had very low hemoglobin levels, 7 and 11.6 Gm. per 100 ml., respectively, on the first day of life and were in immediate distress. Patient 10 developed distress and severe cyanosis on the third day, when these signs may have been related to a congenital cardiac malformation, and the infant was observed to have a hemoglobin of 12 Gm. per 100 ml. with 78 nucleated red cells per 100 white blood cells. Case 3 had a relatively mild anemia with a hemoglobin of 14.5 Gm. per 100 ml.; this infant had only a focal renal lesion, the mildest in the group.

**Fig. 1.** Case 2. Patchy, hemorrhagic cortical necrosis.

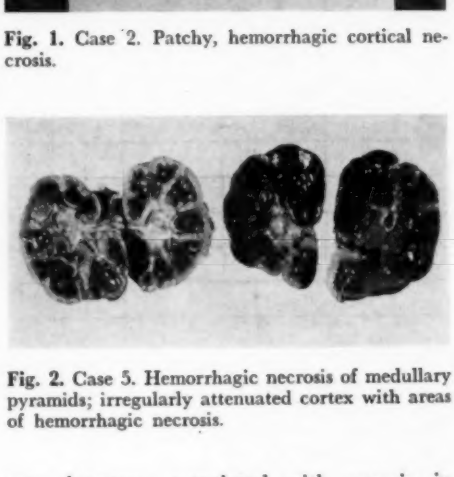


**Fig. 2.** Case 5. Hemorrhagic necrosis of medullary pyramids; irregularly attenuated cortex with areas of hemorrhagic necrosis.

Two other infants with anemia (Cases 7 and 11) appeared to have a hemolytic anemia. In Case 7 there was A-O incompatibility with a positive indirect Coombs test and mild erythroblastosis fetalis. The infant also developed hematoperitoneum due to a ruptured subcapsular hepatic hematoma, probably accounting in this manner for most of his blood loss. Case 11 did not present any evidence of isoimmunization, but this infant had a positive blood culture for *Escherichia coli,* and evidence of meningitis was found at postmortem examination.

Elevation of nucleated red blood cell counts was variable. The count was not elevated in the infant with erythroblastosis and ruptured hepatic hematoma, indicating that acute blood loss may have played the major role in producing anemia. Counts were also elevated, when determined, in the other anemic infants, indicating that blood loss may have preceded delivery by a variable period of time. Two infants with intrauterine asphyxia (Cases 4 and 5) also had elevated counts.

Anuria was specifically mentioned in the clinical records of Cases 6, 7, and 8. No urination was recorded in Cases 1 and 2, but its absence was not specifically mentioned. Hematuria, gross or microscopic, was observed in 5. Only one case, that with the mildest lesion, did not have either anuria or hematuria. Elevation of blood urea nitrogen was seen when values were determined; Case 5 had a level of 75 mg. per 100 ml. and Case 11 a level of 60 mg. per 100 ml.

The clinical appearance of these infants was generally that of lethargy, flaccidity, and progressive dyspnea and apnea. Those who were anemic were often pallid, and cyanosis was reported in both anemic and nonanemic infants. Slight jaundice was observed in Cases 3, 4, and 10. The highest total bilirubin level recorded was 11.4 mg. per 100 ml. in Case 3. Cutaneous petechiae were present in Cases 4, 7, and 11, and bleeding from the mouth and nose was present in Case 4, in whom the platelet count was only 49,140 per cubic millimeter. Clinical evidence of sepsis was present in only Case 11, the only child who was febrile. In Case 10, congenital heart disease dominated the clinical picture.

Case 2 warrants special mention because the baby inadvertently received an excessive amount of heparin during the surgical repair of a diaphragmatic hernia. He suffered postoperatively from generalized hemorrhage, and his blood appeared to be incoagulable. The operation had been done at the age of 8 hours, and he died at 31 hours before corrective measures could be undertaken.

## PATHOLOGIC OBSERVATIONS

The renal necrosis was generally bland and usually hemorrhagic. It was cortical in 4 instances, predominantly medullary in 6, and combined in 1. Renal weight was slightly increased in several and was otherwise within the normal range (Table II).

Cortical necrosis (Cases 1, 2, 4, and 7) varied in its distribution from patchy to diffuse (Fig. 1), and in Case 4 one kidney was diffusely involved whereas only small, focal lesions were present in the other kidney. The intralobular cortical vessels were engorged with blood in all, and the glomeruli were also congested. Extravasation of blood was present in all, but was relatively mild in Case 7. Hemorrhage at the corticomedullary junctions extended into the adjacent bases of the medullary pyramids, except in Case 7.

Generalized medullary necrosis was observed in Cases 5, 9, 10, and 11 and was associated with intense medullary congestion and hemorrhage. Focal, hemorrhagic papillary necrosis was seen in Cases 3 and 6, in the former the mildest lesion of the group. In several with medullary necrosis (Cases 5 and 10), the vessels extending into the cortices along the medullary rays were also engorged, and in Case 5 there was relatively severe involvement with necrosis extending into the attenuated cortex (Fig. 2). Moderate cortical necrosis, with relatively severe tubular necrosis, was observed to accompany the medullary lesion in Cases 9 and 10.

In one instance (Case 8), patchy areas of hemorrhage and necrosis were present in both the cortex and the medulla. The two

**Table II.** Pathologic observations

| | *Renal lesions* | | | | |
|---|---|---|---|---|---|
| *Case No.* | *Renal weight* | *Normal weight* (grams)* | *Distribution of necrosis* | *Thrombi* | *Cortical involvement in cases of medullary necrosis* |
| 1 | 32 | 19 | Cortical, diffuse | None | -- |
| 2 | 50 | 26 | Cortical, patchy | Occasional fibrin strands in cortical arterioles | -- |
| 3 | 8 | 12 | Papillary, focal | None | None |
| 4 | 13R and 11L | 23 | Cortical, diffuse (R) focal (L) | Rare glomeruli and afferent arterioles | -- |
| 5 | 29 | 18 | Medullary, diffuse | None | Extensive |
| 6 | 30 | 23 | Papillary, focal | Fibrin deposits in necrotic medullary vessels | None |
| 7 | 26.5 | 39 | Cortical, diffuse | Fibrin strands in necrotic cortical vessels | -- |
| 8 | 15 | 19 | Cortical and medullary, patchy | Fibrin strands in necrotic cortical vessels | Patchy |
| 9 | 31 | 21 | Medullary, diffuse | None | Irregular |
| 10 | 34 | 21 | Medullary, diffuse | None | Variable |
| 11 | 47.5 | 22 | Medullary, diffuse | None | Tubular, slight |

*Normal weights estimated from figures of Potter & Adair.[28]

zones were not continuous, but the lesions otherwise corresponded to the patterns observed in the other cases.

Occlusive thrombi were observed in only Case 4, in which fibrinous plugs seemed to be present in 1 or 2 capillary loops of occasional glomeruli. The thrombi were far from numerous, and none was seen in larger vessels. Occasional fibrinous strands could be seen in necrotic vessels in other kidneys, but thrombi did not fill the lumens. Thrombi were not seen in the medullary pyramids except in Case 6, and venous thrombi were not observed. Arterial embolization with segmental renal infarction was not included in this particular series of cases.

Leukocytes were only rarely present in or around the areas of necrosis, and in no instance was evidence of renal infection observed. As might be expected, congestion and hemorrhage were often most pronounced at the peripheries of the necrotic areas. The blandness of the lesions also served to distinguish them from "bilirubin infarcts." There was no evidence of inclusion disease of any kind.

The cortical necrosis was predominantly within the inner cortex, with a peripheral zone of sparing (Fig. 3). The lesions in the focally involved kidney of Case 4, however, were subcapsular in location. The diffuse medullary involvement was most severe at the bases of the pyramids, but papillary sparing was quite variable and necrosis of some entire pyramids was seen in Cases 9 and 11 (Fig. 4). The cases with focal papillary necrosis (Fig. 5) did not have other lesions in the kidneys.

| | Associated extrarenal lesions | |
|---|---|---|
| *Necrosis* | *Hemorrhage* | *Other* |
| Stomach, small intestine, liver, adrenal | Lung, small intestine | |
| Small intestine, liver, adrenal | Heart, lung, stomach, intestine, adrenal, testis, brain, spinal cord | Slight preductal aortic coarctation<br>Diaphragmatic hernia (repaired) |
| Adrenal, brain | Small intestine, brain | |
| Brain | Heart, lung, stomach, intestine, urinary bladder, uterus, brain | Arteriolar thrombi, brain<br>Pulmonary atelectasis with hyaline membrane formation |
| Liver, adrenal, brain | Lung, stomach, intestine, adrenal, brain | |
| Spleen, stomach, liver, adrenal, brain | Splenic trabeculae, stomach, liver, adrenal, thymus, brain | Gastric perforation, repaired<br>Aspiration of amniotic sac contents and slight pneumonia |
| Stomach, intestine, liver | Heart, lung, intestine, diaphragm, skin | Ruptured subcapsular hematoma, liver; hematoperitoneum, 100 cc. |
| Stomach, small intestine, liver, brain; splenic lymphoid depletion | Lung, stomach, intestine, liver, uterus, brain | |
| Spleen, pancreas, liver, adrenal | Heart, lung, stomach, pancreas, brain | |
| Stomach, large intestine, liver, adrenal; splenic lymphoid depletion | Intestine, liver | Congenital heart disease: hypoplastic left atrium, left ventricle, aorta; interventricular septal defect |
| Liver, adrenal | Heart, lung, stomach, liver, adrenal, urinary bladder, thymus, skin, brain | Meningitis, acute |

No developmental abnormalities were observed in the renal parenchyma or vasculature of any case. The interlobular, arcuate, intralobular, medullary, and calycine vessels appeared to be normally arranged and free of underlying disease.

Another histologic finding of interest was the presence of focal areas of necrosis in other organs. Most common were focal hepatic and adrenal necrosis, present in 9 and 8 instances, respectively. The liver lesion was centrolobular, bland, and apparently anoxic. A predilection for one lobe or the other of the liver was not observed, and, as in the kidney, there was no evidence of inclusion disease or other primary inflammatory process. The adrenal lesion appeared to be ischemic and involved predominantly the fetal cortex. Another frequent site of necrosis was the brain, which was involved 5 times. This sometimes took the form of widespread neuronal necrobiosis, and in others there were areas of malacia involving the white matter of the centrum semiovale. Cerebral hemorrhage was also present in Case 4 and was associated with occasional thrombi within small blood vessels. Necrobiosis of the gastrointestinal mucosa was observed 6 times, and there was frequently erosion or shallow ulceration. In Case 11 the mucosa of the stomach and jejunum had a regenerative appearace, and there were scattered small areas of scarring, suggesting a healing erosion. Mucosal erosion of the esophagus was also frequently seen, but it has not been included in the tabulation because of its frequent occurrence in newborn infants. Other sites of focal necrosis included the

**Fig. 3.** Case 4. Ischemic necrosis of inner cortex; relatively sharp line of demarcation at corticomedullary junction. (Hematoxylin and eosin stain. Original magnification ×23.)

**Fig. 4.** Case 11. Necrosis of medulla, including papilla; relatively sharp line of demarcation at corticomedullary junction. (Hematoxylin and eosin stain. Original magnification ×14.)

spleen, where there was often depletion of lymphoid follicles, and in one case the pancreas.

A related abnormality was petechial hemorrhage in many organs. Focal areas of extravasation were variably found in the heart, lungs, gastrointestinal mucosa, connective tissue of the liver, genito-urinary tract, cerebrum, and meninges. They were not associated with vascular lesions and may be regarded as having been anoxic in type.

Pulmonary abnormalities were generally related to poor aeration, as reflected in irregular areas of atelectasis and emphysema. Hyaline membrane formation was present in Case 4, and a slight pneumonia in association with aspirated amniotic sac contents was present in Case 6. Other important associated findings included hematoperitoneum in Case 7 as the result of a ruptured subcapsular hematoma of the liver, severe congenital heart disease with hypoplasia of the left atrium, left ventricle and aorta in Case 10, and acute meningitis, possibly as the result of *E. coli* sepsis, in Case 11. The diaphragmatic hernia in Case 2 and the gastric perforation in Case 6 had been adequately repaired.

## LATE EFFECTS OF RENAL NECROSIS

Two cases, not included in the tabulation, illustrate late results of renal necrosis. One infant had suffered from intrauterine anoxia because of placental abruption and also had a hemoglobin of only 10.8 Gm. per 100 ml. on the first day of life. Gross hematuria was observed on the second day, and although he maintained good urinary output his blood urea nitrogen was always markedly elevated. He died at the age of 24 days from supervening staphylococcal pneumonia and septicemia.

Another infant,* who had been born after a traumatic labor, developed pallor and shock 20 minutes after birth. His hemo-

*We are indebted to Dr. S. Farber, Pathologist-in-Chief, Children's Hospital Medical Center, Boston, for permission to cite this case.

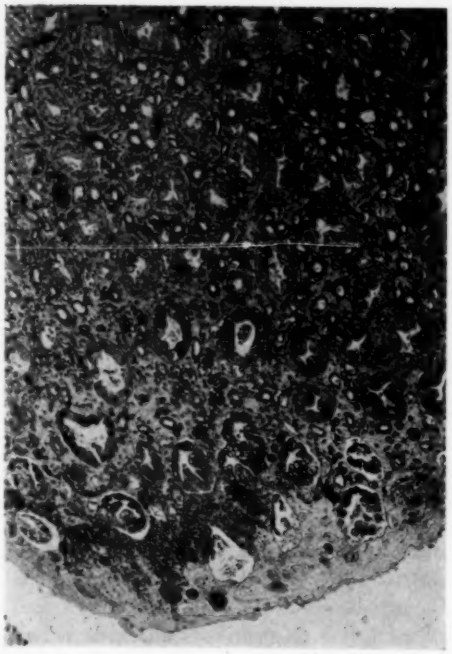


Fig. 5. Case 3. Focal papillary necrosis. (Hematoxylin and eosin stain. Original magnification ×85.)

globin dropped from 10 to 6 Gm. per 100 ml. in several hours, and hematuria was observed on the third day of life. He was mildly oliguric; his blood urea nitrogen rose to 60 mg. per 100 ml. and his serum creatinine was 13 mg. per 100 ml. At the age of 12 days his blood pressure by the palpation method was 220 mm. Hg. He had severe, generalized edema and became markedly oliguric, dying at the age of 23 days.

Both cases had severe renal necrosis, which was predominantly medullary in location, and the cortices were variably atrophic and scarred. The cortical elements were separated by fibrous tissue, and dense scars surrounded disrupted tubules. Many tubules, particularly around areas of medullary necrosis, were lined by tall columnar epithelium, which had an "undifferentiated" or primitive appearance. Many similarly located tubules, which appeared to be part of the collecting system, were the site of squamous metaplasia. The cortical tubules were irregularly atrophic and regenerative, the latter with a tendency to epithelial undifferentiation. The glomeruli were obliterated in

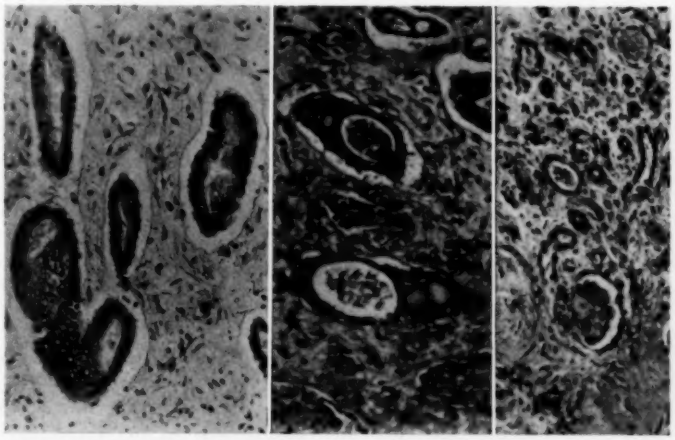


Fig. 6. Patterns of epithelial proliferation in healing necrosis: "primitive ducts" lined by undifferentiated epithelium (left), squamous metaplasia in collecting ducts at margin of necrosis (center), and "primitive glomerulus" in area of cortical scarring (right). (Hematoxylin and eosin stains. Original magnifications: left ×165, center ×210, and right ×150.)

areas of cortical fibrosis, and the remaining glomeruli were fibrotic, solid, or "primitive" in appearance (Fig. 6).

In the first the medullary pyramids were virtually completely necrotic, and a partial line of cleavage, with impending sequestration of the pyramids, seemed to be present in the neighborhood of the corticomedullary junction. Healing necrosis was also present in the liver and adrenals. The cortical atrophy was more severe in the second, in which relatively recent necrosis was also present. The continuing process appeared to be secondary to occlusive vascular lesions. The inter- and intralobular arteries were large and hyperplastic and were the sites of endothelial proliferation, intimal fibrosis, medial hypertrophy, adventitial proliferation, and recent thrombosis and necrosis. Similar arterial lesions, believed to represent a hypertensive arteritis, were also present in the gastrointestinal tract, liver, periadrenal fat, and genito-urinary tract. Resolving necrosis was focally present in the brain and spleen.

In summary then, both cases demonstrate the late morphologic alterations, but in only the second could functional manifestations be attributed to them. The development of malignant hypertension is similar to the course described by Johansmann & Zeek[12] in a newborn infant who had renal necrosis secondary to arterial embolization and by Sharpe and Hall[13] in a 4-month-old infant who had suffered severe intrauterine anoxia. Focal medullary scarring has also been observed by us in the case of a 1-month-old child who was severely asphyxiated at birth, but whether or not the preceding lesion had been the sort of necrosis described above is speculative.

## DISCUSSION

If both hemorrhagic and asphyxial shock may result in a condition of reduced renal blood flow, the cortical necrosis can be reasonably attributed to renal ischemia of sufficient severity and duration. Toxic factors have not been identified, and the pathologic findings do not support a role for infection or vascular thrombi in the causation of the necrosis. Only occasional thrombi were seen in necrotic areas, much like the observations of Sheehan and Davis,[14] who noted that thrombi may develop in necrotic blood vessels after renal ischemia. In experimental conditions, such as the generalized Shwartzman reaction, in which renal cortical necrosis has been attributed to vascular thrombosis, the reaction may be blocked by the use of anticoagulants.[15, 16] In one of our cases the inadvertent administration of heparin resulted in incoagulability of the blood. This did not prevent the development of renal necrosis, but the temporal relationship of the heparinization to the inception of the renal lesion cannot be determined.

Medullary necrosis, on the other hand, has been attributed to medullary vasoparalysis and stasis,[17] in which an element of venous obstruction may be present.[18] Sheehan and Davis[19] have also shown that total renal ischemia due to arterial occlusion in rabbits may lead to cortical necrosis when renal circulation does not become re-established after releasing the arterial clamp. When the period of renal ischemia was somewhat shorter, cortical circulation was sometimes re-established but medullary flow was not. This state led to infarction of the medullary pyramids.

Sheehan and Davis[19] were also able to produce necrosis in just the convoluted tubules by still shorter periods of renal ischemia. A similar gamut of renal lesions has been produced in rats by the administration of serotonin[20, 21] and epinephrine,[21] agents which also act by producing renal ischemia. A spectrum of renal lesions may also occur in newborn infants, in whom tubular necrosis may follow asphyxia neonatorum.[22]

No clinical differences were observed between the group with cortical necrosis and the one with medullary necrosis. No pathologic basis for the distribution of the lesions was observed. In a few cases the necrosis was limited to the medullary papillae, but there was again no obvious reason for this localization.

Petechial hemorrhages and focal areas of necrosis in other organs were especially fre-

quent. These findings may be adduced to support the notion that asphyxia and shock are the underlying abnormalities. The renal lesion was generally the most dramatic and may have been the most significant lethal factor in the majority of cases, but focal areas of necrosis in the liver, adrenal, brain, and gastrointestinal tract were also common. These lesions may be regarded as part of the "syndrome" of neonatal shock.[23]

Renal disease had not, in general, been clinically suspected, and signs were attributed to neonatal anoxia or blood loss. Although there were few clinical findings relating to the urinary system, anuria or hematuria was often present when looked for. These findings, particularly when associated with signs of shock in the newborn, may be a clue to the presence of renal necrosis. Other diagnoses that must be considered under these circumstances are renal vein thrombosis, renal artery thrombosis or embolization, and tubular necrosis.

The reaction to necrosis in the older infants produced certain patterns of epithelial proliferation that have sometimes been regarded as evidence of dysplasia.[24] Regenerating tubules around the areas of medullary necrosis were lined by tall columnar and pseudostratified columnar epithelium, which had a primitive or "undifferentiated" appearance. Some collecting tubules were the site of striking squamous metaplasia. Epithelial retention cysts were also observed in the medullary tissue, but these lacked fibromuscular collars and did not have the appearance of dysplastic elements. Cortical scarring was also associated with epithelial regeneration. Partially involuted glomeruli were occasionally the site of excessive epithelial proliferation, producing so-called primitive glomeruli.[24] These structures appeared to be more reasonably part of the healing process than a form of underlying dysplasia.

The speculation that some dysplastic structures might represent a metaplastic response to inflammation has been offered by Taft.[25] Primitive ductules or tubules and primitive glomeruli can, in our view, be a secondary alteration. This hypothesis is currently being tested by appropriate animal experiments.

## SUMMARY

A review of the clinical material in 11 newborn infants with renal necrosis has disclosed histories that are most often compatible with shock due to severe asphyxia or blood loss. The necrosis was present in both the cortex and medulla, but no underlying malformations were encountered. Focal, ischemic necrosis, and petechial hemorrhage were commonly present in other organs.

Two other infants were observed at approximately 1 month of age, after a similar clinical course in the early newborn period. One developed severe hypertension, and both had severe renal scarring in association with medullary necrosis. Primitive structures, reminiscent of renal dysplasia, developed in association with the healing process and were regarded as a reaction to injury.

## REFERENCES

1. Rubenstein, M., Meyer, R., and Bernstein, J.: Congenital Abnormalities of the Urinary System. I. A Postmortem Survey of Developmental Anomalies and Acquired Congenital Lesions in a Children's Hospital J. PEDIAT. **58:** 356, 1961.
2. Lapage, C. P.: Case of Hemorrhagic Nephritis in a Newborn Baby, Arch. Dis. Childhood **7:** 235, 1932.
3. Campbell, A. C., and Henderson, J. L.: Symmetrical Cortical Necrosis of the Kidneys in Infancy and Childhood, Arch. Dis. Childhood **24:** 269, 1949.
4. Zuelzer, W. W., Charles, S., Kurnetz, R., Newton, W. A., Jr., and Fallon, R.: Circulatory Diseases of the Kidneys in Infancy and Childhood, A. M. A. Am. J. Dis. Child. **81:** 1, 1951.
5. Eskeland, G., and Skogrand, A.: Bilateral Cortical Necrosis of the Kidneys in Infancy, Acta paediat. **48:** 278, 1959.
6. Gardiol, D.: La nécrose de la papille rénale chez le nouveau-né et le nourrisson. Étude anatomo-clinique de 4 cas, Schweiz. Ztschr. allg. Path. **18:** 1212, 1955.
7. Morard, J. C.: Néphrose avec papillo-nécrose hémorrhagique dans un cas d'ictère grave du nouveau-né, J. urol., Paris **61:** 316, 1955.
8. Orth, J.: Ueber das Vorkommen von Bilirubinkrystallen bei Neugeboren Kindern, Arch. path. Anat. **63:** 447, 1875.
9. Boehncke, H.: Beitrag zur Kenntnis des Icterus gravis, Ztschr. Kinderh. **60:** 666, 1939.

10. Bernstein, J., and Landing, B. H.: Extraneural Lesions Associated With Neonatal Hyperbilirubinemia and Kernicterus, Progr. Thirty-first Ann. Meet. Soc. Pediat. Res., Atlantic City, 1961, May 4 to 5, p. 49.
11. Marks, I. M.: Renal Medullary Necrosis Following Exsanguination in Infancy, Lancet **2:** 680, 1960.
12. Johansmann, R. J., and Zeek, P.: Periarteritis Nodosa in a Week-Old Infant, A. M. A. Arch. Path. **58:** 207, 1954.
13. Sharpe, O., and Hall, E. G.: Renal Impairment, Hypertension and Encephalomalacia in an Infant Surviving Severe Intra-uterine Anoxia, Proc. Roy. Soc. Med. **46:** 1063, 1953.
14. Sheehan, H. L., and Davis, J. C.: Renal Ischaemia With Failed Reflow, J. Path. Bact. **78:** 105, 1959.
15. Good, R. A., and Thomas, L.: Studies on the Generalized Shwartzman Reaction. IV. Prevention of the Local and Generalized Shwartzman Reactions With Heparin, J. Exper. Med. **97:** 871, 1953.
16. Shapiro, S. S., and McKay, D. G.: Prevention of the Generalized Shwartzman Reaction With Sodium Warfarin, J. Exper. Med. **107:** 377, 1958.
17. Mandel, E. E., and Popper, H.: Experimental Medullary Necrosis of the Kidney: A Morphologic and Functional Study, A. M. A. Arch. Path. **52:** 1, 1951.
18. Beswick, I. P., and Schatzki, P. F.: Experimental Renal Papillary Necrosis, A. M. A. Arch. Path. **69:** 733, 1960.
19. Sheehan, H. L., and Davis, J. C.: Renal Ischaemia With Good Reflow, J. Path. Bact. **78:** 351, 1959.
20. Waugh, D., and Pearl, M. J.: Serotonin-Induced Acute Nephrosis and Renal Cortical Necrosis in Rats: A Morphologic Study With Pregnancy Correlations, Am. J. Path. **36:** 431, 1960.
21. MacDonald, R. A.: Pathogenesis of Lesions Induced by Serotonin: Nutritional, Vascular, Autoradiographic, and Comparative Studies Using Epinephrine, Am. J. Path. **35:** 297, 1959.
22. Bernstein, J.: Renal Tubular and Pancreatic Islet Necrosis in Newly Born Infants, A. M. A. J. Dis. Child. **96:** 705, 1958.
23. Gruenwald, P.: Asphyxia, Trauma and Shock at Birth, Arch. Pediat. **67:** 103, 1950.
24. Marshall, A. G.: Persistence of Foetal Structure in Pyelonephritic Kidneys, Brit. J. Surg. **41:** 38, 1953.
25. Taft, L. I.: Neonatal Nephritis, Australasian Ann. Med. **5:** 113, 1956.
26. Potter, E. L., and Adair, F. L.: Fetal and Neonatal Death, ed. 2, Chicago, 1949, University of Chicago Press.

# *Effectiveness of adenovirus vaccine in children with repeated acute respiratory illnesses*

**Philip J. Kozinn, M.D.,* Harry Wiener, M.D., and James J. Burchall, M.A.**

BELLE HARBOR, LONG ISLAND, N. Y.

EVERY physician knows how large a role respiratory infections play in his practice, but not every physician is aware of how many of these infections are viral in origin. The actual proportion of respiratory infections caused by bacteria varies a good deal from place to place and from time to time. On the average, however, only 1 of 10 patients suffering from minor respiratory illnesses is likely to have a bacterial infection.[10, 12]

Unfortunately, bacterial infections cannot be differentiated on clinical grounds alone, and the illness is likely to have taken its course when proof of viral etiology is obtained.[9] Prophylactic treatment with effective vaccines is, therefore, of the greatest importance.

The adenoviruses are one of the groups of newly recognized respiratory viruses. Any description of clinical illness caused by adenoviruses must always be subject to the proviso that the same strain of virus may produce one clinical picture in one individual and an entirely different picture in another.[7] As we learn more about these illnesses, however, differences in the clinical patterns produced by individual types are beginning to appear. Type 4 adenovirus infection, for example, has been shown to differ from Asian strain influenza by a more gradual onset, by the presence of pharyngeal inflammation with or without exudate, and by a greater predominance of sore throat and hoarseness among the patient's symptoms.[23, 24]

The clinical syndromes associated with adenovirus infections are currently believed to include pharyngoconjunctival fever,[18, 20] particularly with Type 3 infections; pharyngitis, particularly with Types 1, 2, 3, and 5;[16] acute follicular conjunctivitis;[5] pneumonia;[3] bronchiolitis and laryngotracheobronchitis;[19] and epidemic diarrhea.[11] Experimental inoculation of live Types 3, 4, and 7 adenoviruses into human volunteers produces an acute respiratory illness of about 4 days' duration after an incubation period of 2 to 3 days. This illness is characterized by fever, inflammation of the mucous membranes of eyes, ears, nose, and throat, and by swelling of the cervical lymph nodes.[15]

Adenovirus infections are rare in civilian

*From the Department of Pediatrics, Maimonides Hospital, Brooklyn, N. Y.*

**Address, 141-05 Newport Avenue, Belle Harbor 94, Long Island, N. Y.*

populations, except for occasional outbreaks of respiratory or of conjunctival illness.[13] As in other contagious viral illnesses, there has been growing interest in the possibility of an attenuated living vaccine, but the absence of standardized preparations suitable for mass production suggests that we shall have to make do with killed vaccines for a while longer.[1]

Previous adenovaccine studies have included that of Hilleman.[14] Using adenovirus Types 4 and 7, he reported a significant reduction in acute respiratory infections at a military hospital. Only one case of serologically positive adenovirus disease requiring hospitalization occurred among 311 vaccinated recruits from the second to the fifth week after vaccination, as contrasted to 61 cases among 313 controls. This represents an apparent reduction of 98 per cent from the expected frequency.

A vaccine containing adenovirus Types 3, 4, and 7 has proved highly effective when tested in R.A.F. recruits. There was a total reduction of 40 per cent in the incidence of acute respiratory illness more than one week from vaccination. The protective effect of the vaccine against adenovirus infection was estimated at 70 per cent.[26]

Two recent studies deal with the effect of adenovirus vaccine on children suffering from various allergies. Chobot[4] was unable to evaluate the clinical efficacy of the vaccine, but demonstrated that intradermal injection produced higher antibody titers than did subcutaneous injection. Dees[6] noted improvement in 71 of 96 allergic children treated with adenovirus vaccine by subcutaneous injection. She found no constant relationship between clinical improvement and rise in virus neutralizing antibody titer.

Bell[2] at Great Lakes Training Center vac-

**Table I.** Summary of serologic data

| | *Type 1* | *Type 2* | *Type 3* | *Type 4* | *Type 5* | *Type 7* |
|---|---|---|---|---|---|---|
| **Geometric means of titers of total group** | | | | | | |
| Prevaccination | 21 | 37 | 8 | 8 | 9 | 8 |
| Postvaccination | 29 | 37 | 20 | 31 | 11 | 14 |
| **Geometric means of individual fold increases** | | | | | | |
| | 1.23 | 1.02 | 2.69 | 4.56 | 1.12 | 2.51 |
| **Per cent of group with twofold or greater increase in titer** | | | | | | |
| | 25 | 18 | 47 | 57 | 16 | 33 |
| **Per cent of patients with titers** | | | | | | |
| | < 8 | 8-32 | 32-512 | 512-2048 | | |
| *Type 1* | | | | | | |
| Prevaccination | 52 | 11 | 31 | 6 | | |
| Postvaccination | 50 | 8 | 31 | 11 | | |
| *Type 2* | | | | | | |
| Prevaccination | 39 | 10 | 39 | 12 | | |
| Postvaccination | 37 | 16 | 43 | 4 | | |
| *Type 3* | | | | | | |
| Prevaccination | 62 | 27 | 11 | 0 | | |
| Postvaccination | 32 | 35 | 31 | 2 | | |
| *Type 4* | | | | | | |
| Prevaccination | 46 | 51 | 3 | 0 | | |
| Postvaccination | 24 | 33 | 40 | 3 | | |
| *Type 5* | | | | | | |
| Prevaccination | 64 | 18 | 16 | 2 | | |
| Postvaccination | 68 | 12 | 14 | 6 | | |
| *Type 7* | | | | | | |
| Prevaccination | 71 | 25 | 4 | 0 | | |
| Postvaccination | 36 | 44 | 20 | 0 | | |

**Table II.** Titer rise in specific adenovirus serotypes—relation to prior adenovirus injection

| *Group of patients* | *Total No. of cases* | *Adenovirus serotype* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *1* | | *2* | | *3* | | *4* | | *5* | | *7* | |
| | | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| Prior adenovirus* | 16 | 5 | 31.3 | 4 | 25.0 | 9 | 56.3 | 16 | 100 | 0 | 0 | 13 | 81.3 |
| No prior adenovirus | 68 | 14 | 20.6 | 10 | 14.7 | 23 | 33.8 | 28 | 41.2 | 10 | 14.7 | 16 | 23.5 |

*Four of the "prior adenovirus" group of 20 and 6 of the "no prior" group of 74 patients are not included in this table due to lack of a postvaccine blood sample.

cinated nearly 4,000 recruits with a trivalent adenovirus vaccine and measured the rise in virus-neutralizing antibody titer. The vaccine induced a substantial antibody response to each of the three types of virus contained in it. A significant reduction in the incidence of acute febrile respiratory disease associated with Type 4 was noted.

At present, it seems unlikely that there is need for the use of adenovirus vaccines in the general population,[22, 25] with the exception of specially exposed groups such as recruits newly brought together in Army camps.[8] Children, however, represent a special case with regard to adenovirus infections. We do not know the incidence of these infections and what deleterious effects may follow in their train. Estimates for the frequency of adenovirus infections in children away from the home environment vary between 5 and 10 per cent of all respiratory tract illnesses.[21] A review of the occurrence of adenovirus infections in civilian populations has led to the estimate that use of a completely effective adenovirus vaccine would result in only a 6 per cent reduction in the number of common respiratory infections experienced by an average child during the first 10 years of life.[17]

## METHODS

The vaccine under trial was a polyvalent vaccine with adenovirus serotypes 1, 2, 3, 4, 5, and 7 of the adenopharyngeoconjunctival viruses grown on monkey kidney tissue and inactivated with formaldehyde.* The potency of this vaccine had been determined in animals. It was administered to 104 children, 10 of whom were over 1 and under 2 years of age; 45, aged 2 to 5 years; 36, aged 6 to 9; and 13, aged 10 or more. The children were selected for this study on the basis of a past history of repeated acute respiratory infections over a period of several years at a rate higher than that normally seen in our practice. In a number of these children a variety of measures intended to give relief had been undertaken with little hope of success, and indeed with no success. They included autogenous and influenza vaccines, gamma globulin injections, antibiotics, tonsillectomy, and changes in residence. Twenty children in this group had received adenovirus vaccine comprising serotypes 3, 4, and 7 one year before this trial.

It is quite possible that such selection of patients may bias the study against good antibody response, since most individuals spontaneously develop a greater resistance to respiratory infections than did the present series of patients. The reason for this method of selection was that these are the patients most likely to be given prophylactic vaccines against respiratory viruses. This study aims to help the physician predict what is likely to be the antibody response to injection with a hexavalent adenovirus vaccine in a group of this type.

Each patient was given 2 subcutaneous injections of vaccine, one month apart. Those under 8 years of age received 0.5 c.c. in each injection. Those 8 years old and over received 1.0 c.c. per injection. A blood sample was drawn immediately before the initial vaccination and again 30 days after the second injection. Eighty-four children co-

*This material was kindly supplied by Dr. Charles F. Weiss, Department of Clinical Investigation, Parke, Davis & Company.

operated in these serologic studies. Serum specimens were coded, frozen, and sent by air to the Parke, Davis & Company, Detroit, for measurement of virus neutralizing antibody titers. Titers of antibodies to all the 6 serotypes contained in the vaccine were determined.

An individual monthly follow-up was completed by the same examiners for each child who received the vaccine. The same mimeographed questionnaire was completed at each visit. The number, type, and severity of respiratory infections were recorded for each month and totaled at the end of a year. A successful clinical follow-up was achieved in 102 of the 104 patients who participated in this study.

## RESULTS

Table I summarizes the results of this study. It can be seen that the vaccine produced no definite increase in titers of antibodies to adenovirus serotypes 1, 2, and 5; produced moderate increases to Types 3 and 7; and produced increases averaging fourfold or more to only 1 of the 6 serotypes in the vaccine, Type 4.

There was almost a complete absence of local or constitutional reactions to these injections.

There was no significant change in the number and severity of respiratory illnesses in these patients in the year following the first injection of the vaccine as compared with the preceding year.

Table II compares the rise in antibody titers in those patients who had prior adenovirus vaccine with those who had not been vaccinated before the present investigation. In all cases the group who had received adenovirus vaccine previously had a higher percentage of individuals with rises in a specific serotype than the group who had not received such vaccine. It should be noted that there was also a higher percentage of raised titers to serotypes 1 and 2 which were not contained in the original vaccine among the group which had previously received the adenovirus vaccine. Prior injection in the preceding year of serotypes 3, 4, and 7 was of no apparent clinical advantage to the patients. There was no constant relationship between clinical improvement and rise in virus neutralizing antibody titer.

## SUMMARY

One hundred and four pediatric patients with a history of repeated respiratory illnesses were inoculated with a hexavalent adenovirus vaccine. It failed to produce significant antibody response in a large proportion of the patients. Unless and until a large-scale controlled study shows statistically significant increases in antibody titer and decreases in respiratory illness attributable to the use of this vaccine, there is not sufficient evidence to justify its routine use in pediatrics.

Dr. Benjamin Kramer, Dr. Philip Cohen, Dr. David Grob, and Dr. Israel Schmierer made valuable suggestions in the preparation of this manuscript.

## REFERENCES

1. Adenovirus Vaccination (annotation), Lancet **2:** 182, 1960.
2. Bell, J. A., Hannover, M. J., Heuner, R. J., and Loosli, C. G.: Efficacy of Trivalent Adenovirus (APC) Vaccine in Naval Recruits, J.A.M.A. **161:** 1521, 1956.
3. Chany, C., Lepine, P., LeLong, M., Le Tan Vinh, S. P., and Virat, J.: Severe and Fatal Pneumonia in Infants and Young Children Associated With Adenovirus Infection, Am. J. Hyg. **67:** 367, 1958.
4. Chobot, R., Goldzier, S. E., II, Schwartz, T., and Osborne, D.: Antibody Titer in Allergic Children Given Adenovirus Vaccine, J. Allergy **30:** 97, 1959.
5. Cockburn, T. A., Rowe, W. P., and Huebner, R. J.: Relationship of the 1951 Greeley, Colorado, Outbreak of Conjunctivitis and Pharyngitis to Type 3 APC Virus Infection, Am. J. Hyg. **63:** 250, 1956.
6. Dees, S.: Personal communication.
7. Denny, F. W.: Viruses Newly Isolated From the Upper Respiratory Tract, Pediat. Clin. North America **7:** 295, 1960.
8. Adenovirus vaccine (editorial) Brit. M. J. **2:** 152, 1958.
9. Eichenwald, H. F.: Infections Due to Adenoviruses, Pediatrics **20:** 1108, 1957.
10. Evans, A. S.: Acute Respiratory Disease in University of Wisconsin students, New England J. Med. **256:** 377, 1957.
11. Gardner, P. S., McGregor, C. B., and Dick, K.: Association Between Diarrhoea and Adenovirus Type 7, Brit. M. J. **1:** 91, 1960.

12. Grieble, H. G., Jackson, G. G., Dowling, H. F., Seketa, D. H., and Anderson, T. O.: The Etiology of Common Respiratory Infections in a Civilian Adult Population, Am. J. M. Sc. 235: 245, 1958.
13. Grist, N. R., Sommerville, R. G., and Carson, H. G.: Respiratory Virus Infections in Hospital and in General Practice, 1954-1956, Brit. M. J. 1: 378, 1957.
14. Hilleman, M. R.: Adenovirus Vaccine, A. M. A. Arch. Int. Med. 101: 47, 1958.
15. Hilleman, M. R., Hodges, R. E., Warfield, M. S., and Anderson, S. A.: Acute Respiratory Illness in Volunteers Following the Intramuscular Administration of Live Adenovirus, J. Clin. Invest. 36: 1072, 1957.
16. Huebner, R. J., Rowe, W. P., and Chanock, R. M.: Newly Recognized Respiratory Tract Viruses, Ann. Rev. Microbiol. 12: 49, 1958.
17. Jordan, W. S., Jr.: Occurrence of Adenovirus Infections in Civilian Populations, A. M. A. Arch. Int. Med. 101: 54, 1958.
18. Kendall, E. J. C., Riddle, R. W., Tuck, H. A., Rodan, K. S., Andrews, B. E., and McDonald, J. C.: Pharyngo-conjunctival Fever; School Outbreaks in England During the Summer of 1955 Associated With Adenovirus Types 3, 7, and 14, Brit. M. J. 2: 131, 1957.
19. Morrison, B., Bass, D., Davis, J. A., Hobson, D., Madsen, T. I., and Masters, P. L.: Acute Lower-Respiratory Infections in Children, Lancet 2: 1077, 1957.
20. Parrott, R. H.: Newly Isolated Viruses in Respiratory Disease, Pediatrics 20: 1066, 1957.
21. Parrott, R. H.: Adenovirus and Parainfluenza Virus Infections, Pediat. Clin. North America 7: 965, 1960.
22. Pereira, H. G.: Adenoviruses, Brit. M. Bull. 15: 225, 1959.
23. Schultz, I., Gundelfinger, B., Rosenbaum, M., Woolridge, R., and De Berry, P.: Comparison of Clinical Manifestations of Respiratory Illnesses Due to Asian Strain Influenza, Adenovirus, and Unknown Cause, J. Lab. Clin. Med. 55: 497, 1960.
24. Schultz, I., Stille, W. T., Gundelfinger, B. F., and Miller, L. F.: Combinations of Asian Influenza Virus and Adenovirus Vaccine in the Prophylaxis of Respiratory Illness of Navy Recruits, Am. J. Public Health 50: 543, 1960.
25. Stovin, S.: Sporadic Acute Respiratory Infections in Adults With Special Reference to Adenovirus Infections, J. Hyg. 56: 404, 1958.
26. Wilson, J. S., Grant, P. J., Miller, D. L., Taylor, C. E. D., and McDonald, J. C.: Trial of Adenovirus Vaccine in Royal Air Force Recruits, Brit. M. J. 1: 1081, 1960.

# *Plasma fibrinogen in the diagnosis of neurogenic hyperthermia*

**Abram Kanof, M.D.* and Bruno W. Volk, M.D.**

BROOKLYN, N. Y.

IT IS well known that a variety of diseases of the brain may cause disruption of the temperature control mechanism, and that children with such disturbances may develop an elevated temperature in the absence of infection.[1, 2] Moreover, when infection does supervene, temperature elevations may continue for an inordinately long time despite obvious subsidence of the infection. The pediatrician is, therefore, confronted with the problem of differential diagnosis between fever due to infection and neurogenic temperature elevations. The limited reliability of the erythrocyte sedimentation rate (ESR) in detection of infection has been noted frequently.[3-8] This limitation is based chiefly on the fact that agglutination of small particles is influenced by a variety of nonspecific factors. Moreover, a clinical study[4] has shown that otherwise normal children may have elevated ESR values.

In a previous study we observed several patients with fever of central nervous system origin who had normal fibrinogen concentrations even when the ESR was accelerated.[9] The diagnostic value of the fibrinogen determination has also been reported in other groups of patients.[10-13] In view of these findings, a systematic study was undertaken to determine whether the plasma fibrinogen level could be used in children to differentiate fever due to infection from neurogenic temperature elevations.

## METHODS

**Selection of patients.** Serial determinations of the plasma fibrinogen and ESR were carried out in 23 children with diseases or syndromes commonly thought to be of central nervous origin. The disease categories include dysautonomia, Tay-Sachs disease, Schilder's disease, hydrocephalus, trauma to the brain, and brain tumor. There were also 5 patients with Sydenham's chorea who, although they did not exhibit fever, were included because of the consideration that in some instances this condition may be nonrheumatic in origin. During each febrile episode the children were examined thoroughly to rule out infection.

The series reported in our previous publication[9] in which normal children were subjected to serial determinations of ESR

*From the Department of Pediatrics and the Isaac Albert Research Institute of the Jewish Chronic Disease Hospital.*

**Address, 80 Linden Boulevard, Brooklyn 26, N. Y.*

and fibrinogen was extended from 7 to 20 cases; in no instance did the plasma fibrinogen rise above normal values in a normal child.

The corrected ESR was determined by the method of Wintrobe.[5] The fibrinogen determinations were carried out by the method of Losner and Volk.[8] This procedure is as follows:

Venous blood is withdrawn and added in a ratio of 9:1 to 0.1 M. solution of sodium citrate. After centrifugation 0.1 ml. of plasma and 0.1 ml. of fresh rabbit brain thromboplastin is placed in a cuvette measuring 6 mm. in diameter and 7.5 cm. in length. The mixture is then incubated in a water bath at 37° C. for 3 minutes. Thereafter, the cuvette is placed into the microadapter of a Coleman Junior Spectrophotometer Model 6A with the wave length set at 500 m$\mu$, and 0.1 ml. of 0.02 M. solution of calcium chloride is blown swiftly into the cuvette. At this point, the optical density is read from the upper (optical density) scale and recorded. At the instant of clotting the galvanometer light beam suddenly begins to move to the left. The final optical density is read and recorded, and the first value is substracted from the second reading. The difference, multiplied by 100, is termed "clot density." From this value the fibrinogen level is calculated according to the following, previously elaborated formula ($F = 18d + 120$) where F indicates fibrinogen in milligrams per 100 ml. of plasma and d represents the clot density. The clot density in normal persons of either sex ranges from 5 to 15, corresponding to a fibrinogen concentration ranging from 210 to 390 mg. per 100 ml.

## CASE REPORTS

**Fibrinogen in dysautonomia.** The identification of central neurogenic fever is especially important in patients with dysautonomia because these patients are also particularly prone to respiratory infections. The following 6 case reports are of typical patients with this syndrome in whom dissociation of ESR and fibrinogen, i.e., a normal plasma fibrinogen value in the presence of an elevated ESR was very helpful. The graphs of only 2 cases are reproduced.

*Case No 1.* J. R. was a 4-year-old boy with typical dysautonomia. He exhibited the unpatterned type of temperature elevation which we have designated as the athetoid type. Fig. 1 represents the course of disease for a representative period of 45 days.

*Case No. 2.* S. B. was an 18-month-old female infant with dysautonomia (Fig. 2). The tendency to high "athetoid" temperature elevations was particularly marked. During the early period of unexplained fever, the ESR was considerably elevated while the fibrinogen level remained normal. During the third week of the hospital stay she developed pneumonia; the fibrinogen level rose sharply and declined quickly to normal when the pneumonic process resolved. The ESR continued to be elevated. A second attack was accompanied by a similar ESR-fibrinogen dissociation.

*Case No. 3.* K. S. was a girl of 14 years. It had been noted since birth that her very fair skin blotched easily and that there was an absence of lacrimation. She had 12 episodes of pneumonia between 1 and 9 years of age. There was a mild degree of mental retardation. On admission she had a blood pressure of 200/145. The hypertension was quite labile and was greatly influenced by posture. The diagnosis of pheochromocytoma was ruled out by operation.

Fever was not a prominent feature in this patient. She did have slight temperature elevations ranging from 100.4° to 101.6° F. on 11 occasions including the day after exploration for the presence of a pheochromocytoma when the fever rose to 102° F. Each time the ESR remained elevated throughout, while the fibrinogen value remained steadfastly normal.

*Case No. 4.* M. W. was a 7-year-old boy with typical dysautonomia. He was admitted in May of a given year with a normal temperature. In August, during a hot spell and with no evidence of infection there began a daily temperature rise to 102° F. This febrile pattern continued until well into September when cool weather intervened. Five ESR

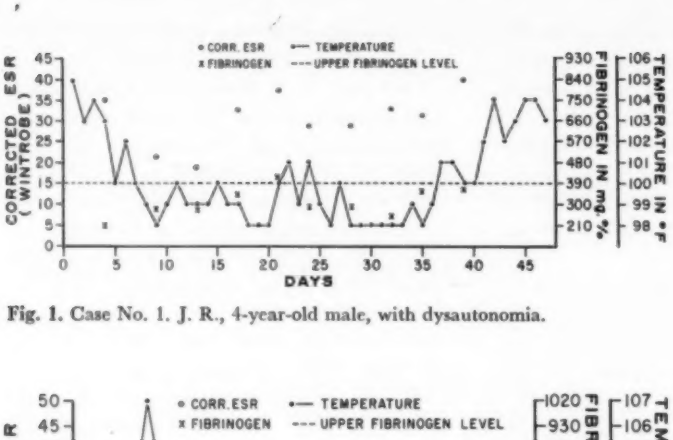



**Fig. 1.** Case No. 1. J. R., 4-year-old male, with dysautonomia.

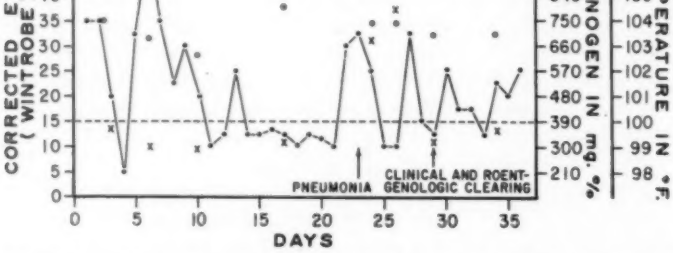



**Fig. 2.** Case No. 2. S. B., 18-month-old female who had dysautonomia with intercurrent pneumonia.

determinations during the febrile period ranged from 30 mm. per hour to 50 mm. per hour. The fibrinogen level was normal each time.

*Case No. 5.* Y. R. was a 2-year-old female admitted with dysautonomia. On the third day after admission the temperature rose to 102° F., and on the fourth day it reached 106° F.; it remained in this range for 3 more days when she died. On the first and third days of the temperature elevation, the ESR was 33, and the fibrinogen value was 354 mg. per cent. Careful postmortem examination revealed no evidence of infection.

*Case No. 6.* R. K. was a 19-month-old female with dysautonomia. At 6 months of age she began to manifest high, irregular, unexplained "athetoid" type of temperature. In this patient, however, on 7 occasions when the temperature was above 102° F., both ESR and fibrinogen values were normal. Only once when the fever was associated with acute pharyngitis was there a moderate elevation of both tests. This is the only case in our series of patients with dysautonomia in which despite fever, the ESR as well as the fibrinogen level remained normal, and there was no dissociation of the two.

**Fibrinogen levels in Tay-Sachs and Schilder's disease.** On our Tay-Sachs ward, serial fibrinogen determinations are carried out routinely to identify fever of central origin. Fig. 3 summarizes 3 typical examples. In Cases 7, 8, and 9, M. S., A. D., and V. R., respectively, there were temperature elevations, but no evidence of infection. Although the ESR was elevated each time, the fibrinogen values remained within normal limits.

*Case No. 10.* J. D. was a patient with Schilder's disease in whom 5 random episodes were charted (Fig. 4). The first episode showed a period of normal temperature with an elevated ESR, a finding not rare in

children free of infection.[4] The fibrinogen level, however, was normal. This dissociation became especially marked when the temperature rose. Four such episodes are charted. Each time, the ESR rose to even higher levels, but the fibrinogen level remained within normal limits. In all these instances the febrile reactions were not associated with any determinable infection.

**Hydrocephalus, brain tumor, and brain trauma.** Study of the ESR and the fibrinogen level is useful in patients with hydrocephalus with or without meningomyelocele. These patients are notoriously subject to infections. Injection of air or radiopaque material into the subarachnoid space may result in temperature elevations. The presence or absence of ESR-fibrinogen dissociation may help in deciding whether a given temperature elevation is the first sign of infection. Fig. 5 illustrates the data of 3 of 5 patients with this condition in whom such studies were found very useful.

*Case No. 11.* D. S. was admitted for spina bifida with meningomyelocele and hydrocephalus. Achromycin, 50 mg. daily, was administered prophylactically; there was never any evidence of meningeal or respiratory infection. She finally developed diarrhea which lasted for a few days, and then a terminal bronchopneumonia. Unfortunately serial determinations of ESR and fibrinogen lapsed during these final few days so that in this instance we cannot report the effect of the terminal pneumonia on the fibrinogen level.

*Case No. 12.* L. T. was a 9-year-old boy with hydrocephalus. On 2 occasions when the child was febrile, the physical examination and urinalysis were within normal limits. Dissociation of the ESR and the fibrinogen level existed each time.

*Case No. 13 S. R.* After several bypassing surgical procedures for obstructive hydrocephalus had not been successful, it was decided to treat the patient with repeated subdural taps. Each procedure was followed by a rise in the temperature associated with an elevated ESR. However, as long as physical examinations, urinalyses, and careful bacteriologic examinations of the dural fluid were normal, the fibrinogen levels remained within normal limits. The subdural tap on the twentieth day was followed by a spiking temperature, this time accompanied by an elevation of the fibrinogen concentration. Culture of the subdural fluid was positive for staphylococcus aureus.

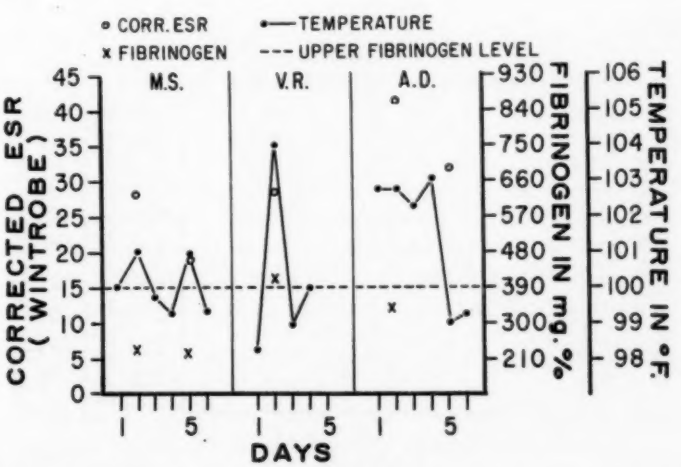



**Fig. 3.** Cases Nos. 7, 8, and 9. Isolated febrile incidents in 3 patients with Tay-Sachs disease.

*Case No. 14.* R. M. was a child with meningomyelocele which was successfully repaired on the first day of life. However, he developed progressive hydrocephalus and had numerous bouts of unexplained fever, ranging up to 105° F. On 5 occasions, when the temperature was well above normal, the ESR and fibrinogen were both normal. On the sixth occasion there was a rise in temperature to 102.5° F. following smallpox vaccination. The ESR rose to 25 mm. per hour, while the fibrinogen level remained at 354 mg. per cent.

*Case No. 15.* F. B. was a 2-year-old child who fell from a high chair and had severe cerebral hemorrhage. On admission to our service he had little more than vegetative function. He exhibited an "athetoid" fever curve but as long as there was no infection there was ESR-fibrinogen dissociation.

*Case No. 16.* D. C. was a baby with congenital cerebral injury and a tendency to have high fever irregularly in the absence of infection. There usually was ESR-fibrinogen dissociation, but occasionally both tests remained within normal limits despite high fever.

*Case No. 17.* This infant had congenital cerebral agenesis and a constant moderately elevated temperature. On 4 occasions on which the tests were performed during such bouts of unexplained fever, both ESR and fibrinogen were normal.

*Case No. 18.* J. F. was a 9-year-old girl admitted after an operation for glioma of the brain stem with recurrence and extension into the hyothalamus (Fig. 6). She exhibited persistent hyperthermia, increasingly frequent convulsions, and progressive lethargy. To test the patency of the cerebrospinal circulation an injection of albumin $I^{131}$ was made into one ventricle. There followed a period of extremely high "athetoid" type of fever. The ESR was constantly elevated, but the fibrinogen level was elevated only once, 2 days after the injection; it remained normal thereafter. When, terminally, she developed pneumonia, the fibrinogen rose to extremely high levels. This occurred despite the fact that in the terminal state the pneumonia did not produce fever.

**Fibrinogen levels in Sydenham's chorea.** We have included Sydenham's chorea in this study because, although these patients do not ordinarily have fever, nor did ours, there is still a question whether all such patients have a rheumatic infection or whether in some the chorea is due to other, possibly psychiatric, causes. Efforts to separate 2 types of chorea on the basis of ESR determinations have not been successful. These patients were studied during clinical investi-

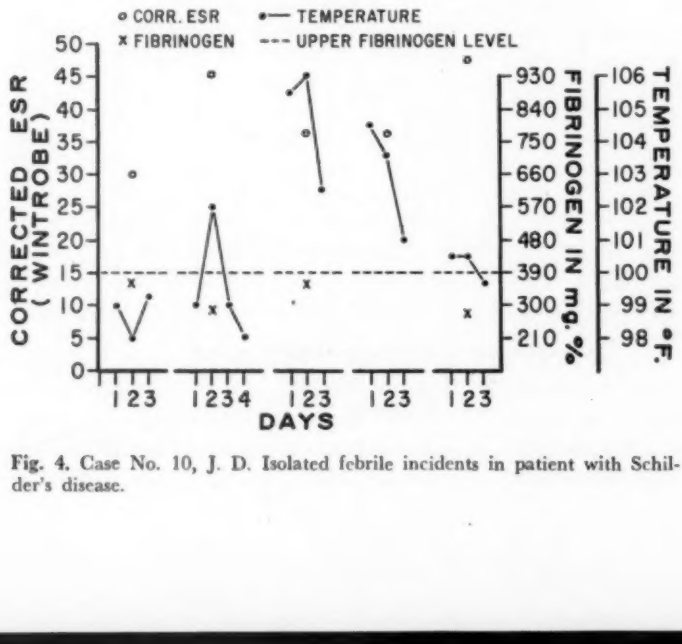



Fig. 4. Case No. 10, J. D. Isolated febrile incidents in patient with Schilder's disease.

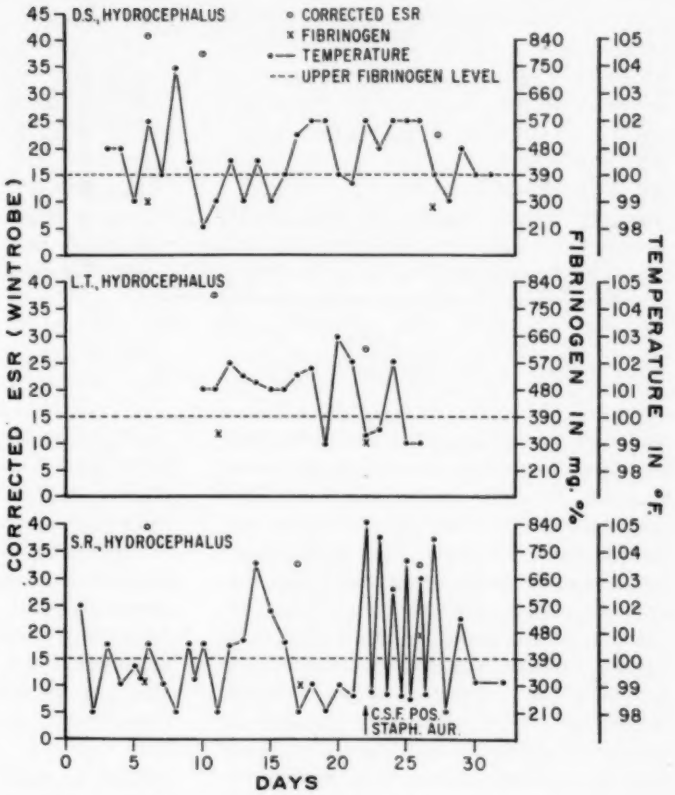



**Fig. 5.** Cases Nos. 11, 12, and 13. Hydrocephalus. Case S. R., intercurrent staphylococcal meningitis.

gation of the value of cortisone in the treatment of this disease. Our group included 5 children with typical Sydenham's chorea in whom careful study, including serial electrocardiograms and extensive follow-up, revealed no evidence of rheumatic infection. All patients received Meticorten therapy. As is usually the case, these children manifested no fever except occasionally as a "rebound" phenomenon when hormonal treatment was withdrawn. Serial ESR and fibrinogen determinations were performed.

*Case No. 19.* P. R. was a 12-year-old girl admitted with a recurrence of chorea 5 years after a previous attack (Fig. 7). She had no evidence of cardiac abnormality during the hospital stay. She was given Meticorten, 100 mg., daily. There was a rapid reduction in abnormal movements. The temperature was normal throughout until the cortisone was discontinued on the tenth hospital day. She then suffered a rebound and the temperature became elevated to 103° F. The ESR determinations prior to this time were consistently elevated, while the fibrinogen level was consistently normal. When the temperature rose on withdrawal of the Meticorten the sedimentation rate rose even higher than before and continued high for weeks. The fibrinogen value increased only slightly and then dropped to normal within 2 days.

*Case No. 20.* M. M. was an 11-year-old girl with chorea. Examination revealed a faint systolic murmur at the apex, but re-

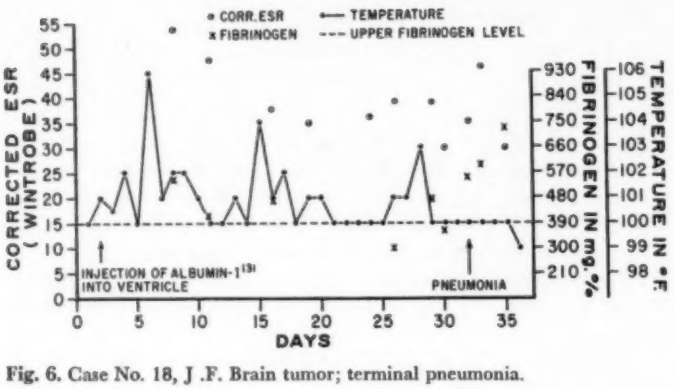



**Fig. 6.** Case No. 18, J .F. Brain tumor; terminal pneumonia.

peated electrocardiograms were normal and there was no clinical evidence of rheumatic infection. At a visit to the follow-up clinic some months later the same murmur was present, but there was no other indication of cardiac or rheumatic involvement. She did display evidences of marked psychologic instability. Improvement on Meticorten was dubious, and she remained on the ward for 4 months. The temperature hovered between 98° F. and 100° F. throughout the stay. A total of 51 ESR and a similar number of fibrinogen determinations were performed. The former varied from normal and moderate rates to high elevations. The fibrinogen levels were normal except for 6 moderate elevations to between 426 and 489 mg. per cent.

*Case No. 21.* J. P., an 11-year-old girl, was admitted with chorea. She displayed definite psychic disturbances before and during the hospital admission. At no time was there any evidence of cardiac involvement or any other signs of rheumatic infection. She was placed on Meticorten 10 days after admission, and this treatment was continued for a period of 2 months, but the therapeutic result was unsatisfactory. The temperature on admission was normal and remained so until the day after the administration of Meticorten was discontinued, when it rose to 101° F. for 2 days. However, at the same time she developed a urinary tract infection, which was treated with sulfisoxazole acetyl. While the temperature elevation may have been due to the rebound following withdrawal of hormonal therapy or to the urinary infection, another increase to 101° F. 2 weeks later was definitely due to a recrudescence of the urinary tract infection.

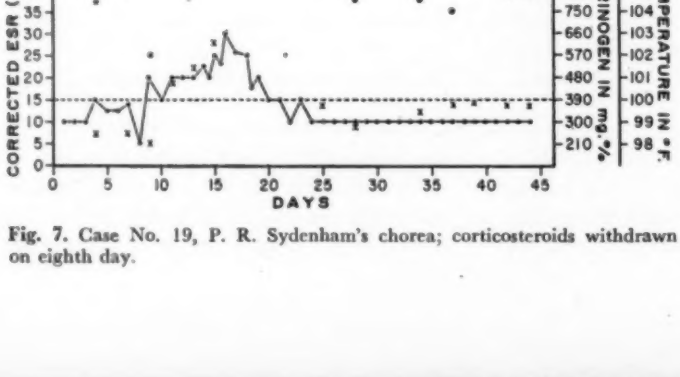



**Fig. 7.** Case No. 19, P. R. Sydenham's chorea; corticosteroids withdrawn on eighth day.

ESR and fibrinogen determinations were obtained every 2 or 3 days; both were within normal limits until 2 days after discontinuance of the Meticorten therapy. Subsequently the ESR rose during each febrile period, whereas the fibrinogen level remained within normal limits. We have noted before that while a mild urinary infection may cause an elevation of the ESR, the fibrinogen value usually remains within normal limits.[9]

*Case No. 22.* K. K. was a 10-year-old girl with chorea. There was no cardiac involvement at any time. She was treated with hydrocortisone which was discontinued with no rebound elevation of temperature but there was nevertheless a rise in ESR. The fibrinogen value remained within normal limits during this rebound. The temperature was normal throughout except for an occasional rise to 101° F. The erythrocyte sedimentation rates were often normal, usually slightly elevated, and accelerated to 40 mm. per hour on 19 occasions. The fibrinogen value rose to 462 mg. per cent once and was well within normal limits on all other occasions.

*Case No. 23.* F. S. was a 12-year-old girl with chorea. There was no cardiac involvement. The temperature was virtually normal throughout the observation. The ESR was slightly accelerated only once, to 24 mm. per hour but the fibrinogen value was only 264 mg. per cent. In 10 additional determinations both the ESR and fibrinogen values were within normal limits.

## DISCUSSION

It is generally agreed on experimental as well as clinical grounds that injury to certain areas of the brain produces temperature elevations indistinguishable from those resulting from infection. In an era when children with severe and diffuse brain involvement can survive for years, the need to distinguish between noninfectious, neurogenic fever and fever due to infection arises frequently.

The ESR is not a reliable index of infection. Statistical studies of Hollinger and Robinson[4] demonstrate that a single Wintrobe report of 30 mm. per hour should be interpreted as any value between 25 and 35 mm. per hour. A subsequent report of 25 mm. per hour could, therefore, be interpreted as a drop of 15 mm. per hour or equally well as no change. To obtain a valid difference of 1 mm. per hour it would be necessary to do 11 tests each day on each patient. Furthermore, while the ESR in healthy children may vary from 0 to 20 mm. per hour, 5 to 10 per cent of apparently well children may have above "normal" values. Finally, they reported that 30 ESR determinations made on one sample of blood by the same method gave variable results. Comparative readings by the 3 generally accepted methods may show variations of as much as 5 mm. per hour.

The lack of reliability of the ESR results largely from the fact that although the fibrinogen concentration of the plasma is the chief factor influencing the settling of the red blood cells,[14] secondary components also influence their suspension stability; these include the various globulins,[15-17] cholesterol,[19] the viscosity of the plasma,[14, 15] the size of the red blood cells,[14, 15] the volume of packed red cells,[5, 6, 19, 20] and the electrostatic charges of the proteins and of the red blood cells.[17] Thus, a method would offer a distinct clinical advantage if it were to determine only the predominant factor involved in the ESR, namely, the fibrinogen content of the plasma.

The plasma fibrinogen did not rise in several cases with Tay-Sachs disease, and one child with Schilder's disease, and in one baby suffering from cerebral necrosis following brain injury.

Five cases of Sydenham's chorea were included in this study not because fever is characteristic of this disease but because the relationship of it to rheumatic infection is not well understood. While many pediatric textbooks assume that Sydenham's chorea is a manifestation of rheumatic infection[20, 21] other texts[22] and some authors[23] consider the relationship of both conditions as an open question. Kagan,[24] after re-evaluating studies on over 6,500 cases, found that the rela-

tionship between rheumatic infection and chorea, generally based on the existence of other rheumatic manifestations, was not conclusive, and that some patients suffered from chorea of nonrheumatic origin. He found the ESR to be of value in differentiating the rheumatic from the nonrheumatic type.

We have already shown that in rheumatic fever the plasma fibrinogen level is a true index of the severity of the infection; it rises during the acute phase and subsides promptly thereafter.[9, 10] Furthermore, when the fibrinogen level decreases to normal values, it tends to remain so except during subsequent infections. On the other hand although the ESR is usually increased during active rheumatic infection, constant or sporadic elevations tend to be manifested long after subsidence of the clinically active phase. In this small series of patients with chorea of the Sydenham type, the lack of cardiac involvement in all and the presence of psychiatric factors in 2, led us to suppose that the disease was not rheumatic in origin. The normal fibrinogen levels tended to support this assumption.

## SUMMARY

This study was designed to compare the erythrocyte sedimentation rate (ESR) and the plasma fibrinogen level as guides in differentiating fever of noninfectious central nervous system origin from that produced by infection. For this purpose, serial determination of the ESR and fibrinogen was carried out in 24 patients with various types of brain involvement, such as dysaoutonomia, Tay-Sachs disease and Schilder's disease, chorea, and hydrocephalus.

In no instance was a high plasma fibrinogen level maintained in the absence of infection. A normal fibrinogen concentration would seem to indicate a central origin for an elevated temperature regardless of whether there is an acceleration of the ESR. It is believed that serial determinations of the plasma fibrinogen concentration may serve as a useful tool in distinguishing fever of noninfectious central nervous system origin from that due to infections.

## REFERENCES

1. Ylppo, L., and Ylppo, A.: Chronic Cerebral Fever in Cerebral Palsy—Temperature Athetosis, Acta pediat. **45:** 483, 1956.
2. Erickson, T. C.: Neurogenic Hyperthermia (A Clinical Syndrome and Its Treatment), Brain **62:** 172, 1939.
3. McFarlane, R. G., and O'Brien, J. R.: The Rationale of the Blood Sedimentation Rate, Practitioner **157:** 1, 1946.
4. Hollinger, N. F., and Robinson, S. J.: A Study of the Erythrocyte Sedimentation Rate for Well Children, J. PEDIAT. **42:** 304, 1953.
5. Wintrobe, M. M., and Landsberg, J. W.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189:** 102, 1935.
6. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1943, Lea & Febiger, pp. 167-168.
7. Meyers, A. J., Trevorrow, V., Washburn, A. H., and Mugrage, E. R.: Quantitative Studies of the Influence of Plasma Proteins and Hematocrit on the Erythrocyte Sedimentation Rate, Blood **8:** 893, 1953.
8. Losner, S., Volk, B. W., Jacobi, M., and Newhouse, S.: Spectrophotometric Studies on Clot Density, J. Lab. & Clin. Med. **38:** 28, 1951.
9. Kanof, A., Losner, S., and Volk, B. W.: Clot Density Method of Fibrinogen Determination in Some Pediatric Conditions, Pediatrics **12:** 564, 1953.
10. Losner, S., Volk, B. W., and Kanof, A.: The Clot Density Determination of Fibrinogen in Rheumatic Fever, Am. Heart J. **50:** 100, 1955.
11. Losner, S., and Volk, B. W.: The Fibrinogen Polymerization Test in Active Rheumatic Disease, Am. J. M. Sc. **229:** 371, 1955.
12. Volk, B. W., Losner, S., Jacobi, M., and Lazarus, S. S.: Studies on Clot Density, Am. J. Clin. Path. **22:** 99, 1952.
13. Losner, S., Volk, B. W., and Wilensky, N. D.: Fibrinogen Concentration in Acute Myocardial Infarction, A. M. A. Arch. Int. Med. **93:** 231, 1954.
14. Fahraeus, R.: The Suspension-Stability of the Blood, Acta med. scandinav. **55:** 1, 1921.
15. Thygesen, J. E.: The Mechanism of Blood Sedimentation, Acta med. scandinav. **134:** 1, 1942.
16. Aldred-Brown, G. R. P., and Munro, J. M. H.: The Sedimentation Rate and the Plasma Proteins, Lancet **1:** 1333, 1934.
17. Ropes, M. W., Rossmeisl, E., and Bauer, W.: The Relationship Between the Erythrocyte Sedimentation Rate and the Plasma Proteins, J. Clin. Invest. **18:** 791, 1939.
18. Kurten, H.: Die Senkungageschwindigkeit der roten Blutkorperchen in ihrer Beziehung zu Cholesterin und Lechithin, Arch. ges. Physiol. **185:** 248, 1920.
19. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variation in the Cell Volume Percentage of Blood, J. Clin. Invest. **8:** 545, 1930.

20. Holt, L. E., and McIntosh, R.: Diseases of Infancy and Childhood, ed. 12, New York, 1953, Appleton-Century-Crofts, Inc., pp. 823-840.
21. Gibson, S.: In McQuarrie, I., and Kelly, V. C., editors: Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Co., Inc.
22. Kuttner, A. G.: In Nelson, W. E., editor: Textbook of Pediatrics, ed. 7, Philadelphia, 1959, W. B. Saunders Company, p. 906.
23. Daniel, W. A., Jr.: Chorea in the Negro Race, J. PEDIAT. **27:** 554, 1945.
24. Kagan, B. M., and Mirman, B.: Sydenham's Chorea, A Syndrome for Differential Diagnosis, J. PEDIAT. **31:** 322, 1947.

# *Liver diseases and osteoporosis in children*

## *I. Clinical observations*

**Ching Tseng Teng, M.D.,* C. William Daeschner, Jr., M.D.,**

**Edward B. Singleton, M.D., Harvey S. Rosenberg, M.D., V. William Cole, M.D.,**

**Leighton L. Hill, M.D., and James C. Brennan, M.D.**

HOUSTON, TEXAS

OSTEOPOROSIS is a common metabolic bone disease in the aged. Its incidence in children, however, is not known. Although its association with liver diseases is well recognized,[1-3] detailed reports of actual cases are conspicuously few in number in the pediatric age group. Severe osteoporosis has been reported in 1 case of glycogen storage disease,[4] 3 cases of hepatic carcinoma,[5, 6] and 1 case of cirrhosis.[6] In Cocchi's series on hepatogenic osteoporosis, there were only 2 infants with *rickets* among 27 of his patients and 62 cases collected from the literature.[7] This paucity of reports is at variance with our observations (Table I).

Our interest in the problem of osteoporosis in infants and children stemmed from our observations of a 2½-year-old girl who had severe osteoporosis and marked growth retardation in association with primary hepatoma. After the tumor was successfully removed, the osteoporosis rapidly improved and the growth in general spurted to normal. In a study of 8 other cases of primary hepatic tumors from our hospitals we found 5 more patients with osteoporosis, and several of these children showed improvement following hepatolobectomy. We then extended our study to 7 cases of glycogen storage disease and 10 cases of chronic hepatitis; and in each series approximately two thirds of the children were found to have generalized osteoporosis; and certain other atrophic changes also occurred in many of them (Table I).

In the latter groups there were also cases showing improvement of osteoporosis when the liver disease was improved.

These observations lead us to believe that a deficit of protein resultant from hepatic dysfunction may be responsible for the development of osteoporosis in these children. The coincidence of muscle atrophy and growth retardation lends support to the thesis.

This report will present the clinical and

*From the Departments of Radiology, Pediatrics, and Pathology, Texas Children's Hospital, Jefferson Davis Hospital, and Baylor University College of Medicine, Houston, Texas.*

**Address, Texas Children's Hospital, Houston, Texas.*

laboratory data and discuss the possible pathophysiologic mechanism by which a deficit of protein may occur in each type of liver disease. A discussion of the hypothesis that hepatogenic osteoporosis and other atrophic changes represent a compensatory mechanism whereby more serious symptoms of protein deficiency are prevented or delayed will be presented in a subsequent paper.

## I. GLYCOGEN STORAGE DISEASE

Five types of glycogen storage disease are now recognized. In this report we are concerned with the classical type only which was first described by von Gierke in 1929.[8]

The clinical and biochemical changes of hepatorenal glycogenosis have been well documented.[9-14] There are considerable variations in the severity of the disease and the prognosis of life expectancy which depend largely upon the degree of enzyme deficit. In those who survive to childhood or adulthood, growth retardation and dwarfism are common. The occurrence of osteoporosis in these patients, however, has rarely been recorded.[4]

In 7 children with von Gierke's disease we have found varying degrees of osteoporosis, growth retardation, and muscle and skin atrophy in 6 cases.

**General observations.** There were 6 boys and 1 girl in this series. Their ages ranged from 3 months to 3 years at the time of diagnosis, and from 4 months to 12 years at the time of the last follow-up.

Four of the 7 patients were within the first year of life when last seen at the Texas Children's Hospital. Even at this early stage of the illness, all but 1 of these infants showed definite evidence of osteoporosis or growth failure. The periods of observation of these infants were too short to forecast with any certainty what the future may hold for them.

Of the other 3 patients, a 4-year-old child (Case 1), who had the most severe disease of the entire group, showed very marked osteoporosis and muscle wasting, was severely retarded mentally, and was bedridden all his life. He had been moribund from hypoglycemic and acidotic episodes innumerable times since the age of 2 months. The prognosis appears hopeless (Fig. 1).

At the other end of the spectrum were 2 brothers (Cases 6 and 7), aged 12 and 6 years, whose disease was relatively mild. They have been reasonably well. Although they have had hypoglycemia, acidosis, hemorrhagic episodes, and various types of infection on a number of occasions, they have responded to appropriate treatment. The mental development has been normal. The physical growth, however, was moderately retarded; the stature being roughly that of boys half their age. The bones were moderately osteoporotic, the muscles poorly developed, the skin delicate and thin (Fig. 2). These observations are summarized in Table II.

**Hepatomegaly and liver function studies.** Moderate to marked hepatomegaly was found in all seven patients. In Case 1 the progression of hepatic enlargement from 2 to 3 cm. to 8 to 10 cm. below the costal margin was noted in the course of 2 months after the onset of symptoms.

The liver function studies were not as complete as one would desire. Nonetheless, the results (Table III) clearly indicated that some impairment of liver function was present in most of our cases. The serum protein concentration showed no significant alteration in 3 of the 4 cases in whom this was determined. A definite decrease in serum albumin level and a reversal of the albumin-globulin (A/G) ratio were ob-

**Table I.** Incidence of osteoporosis in liver diseases in children

| *Disorders* | *Glycogen storage* | *Primary tumors* | *Hepatic cirrhosis* | *Total* |
|---|---|---|---|---|
| Total | 7 | 9 | 10 | 26 |
| Osteoporosis | 6 | 6 | 7 | 19 |
| Growth retardation | 6 | 1 | 3 | 10 |
| Weight loss | | 3 | 4 | 7 |
| Hepatic impairment | 7 | 1 | 10 | 18 |

served in Case 1 in whom marked osteoporosis and growth retardation were prominent findings. Hyperlipemia was a frequent observation.

**Hypoglycemia and acidosis.** Fasting hypoglycemia (varying from 5 to 40 mg. per cent) was noted in all cases. In Case 1 medical attention was first sought because of coma and generalized seizures.

Acidosis was observed in 5 patients, and ketonuria was recorded in 4. In Case 1 these episodes occurred so frequently that the mother had learned to bring the child promptly to the emergency clinic where appropriate therapy usually sufficed to control the incipient symptoms and thus aborted the development of more serious manifestations on many occasions.

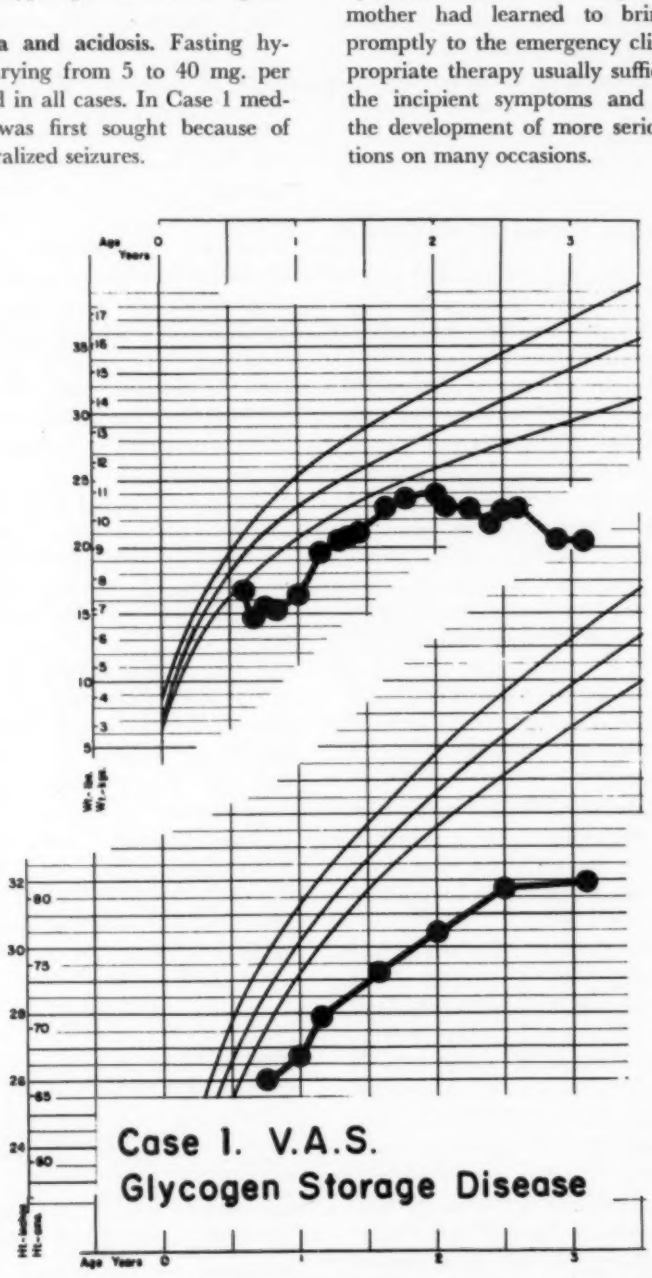



**Fig. 1.** Case 1. Marked retardation of growth. Irregular pattern of weight gain or loss largely attributable to state of hydration at the time of visit.

**Epinephrine and glucagon tolerance tests.** Epinephrine and/or glucagon studies were performed in all of our patients. In every instance a flat curve was obtained. This is shown in Fig. 3.

**Liver biopsy.** Biopsy of the liver was performed in 5 of the 7 patients. In all biopsy specimens the liver cells were enlarged with abundant clear cytoplasm filled with glycogen (Fig. 4). Quantitative enzyme study of the tissue removed was not available.

**Osteoporosis.** The frequent occurrence of osteoporosis, muscle, and skin atrophy, and general growth retardation in our patients have already been alluded to (Table I). The demonstration of multiple transverse linear densities in the shafts of long bones in the older children (Fig. 5) is of interest. They represent periodic disturbances of bone growth, and the intervening normal bone is evidence of resumption of growth during periods of improvement.

The values for serum calcium and phosphorus such as available in a few patients were close to the lower limits of normal. They are difficult to evaluate in view of the presence of acidosis and aciduria. The normal serum alkaline phosphatase levels in these patients, however, are reassuring that rickets need not be considered seriously.

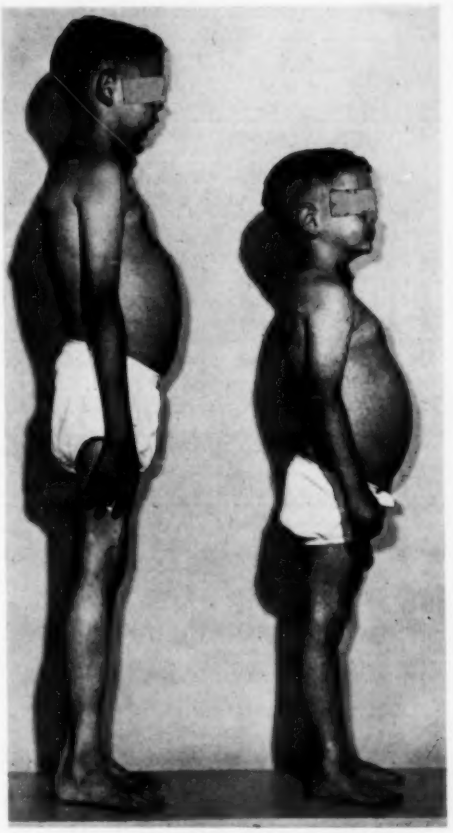


**Fig. 2.** Cases 6 and 7. Two siblings, aged 12 and 6 years, respectively. Weight and height of each considerably below normal average. Note prominent abdomen due to hepatomegaly and nephromegaly, and smallness of musculature, especially of lower extremities.

## II. PRIMARY HEPATIC TUMORS

Primary tumors of the liver in infancy and childhood occur in a variety of anatomic and histologic forms.[15] Of the parenchymal forms, which are most common, 2 types predominate: *(A)* liver cell or embryonal carcinoma with malignant characteristics and early metastasis, and *(B)* primary hepatoma with benign features and often rich glycogen stores. Their occurrence at an early age and the extreme rarity of preexistent cirrhosis suggests that they are different from adult hepatomas.

The reported incidence of simple osteoporosis in children with primary hepatic tumors has been extremely rare.[5, 6]

In 9 children with primary hepatic tumors we have found 6 with osteoporosis. One child (Case 8) had also severe retardation of growth in addition to marked osteoporosis; she made a remarkable recovery after the removal of the tumor. The case history follows.

**Case report.** Case 8. L. L. was a 30-month-old white girl. She was admitted to the pediatric service of the Jefferson Davis Hospital on March 1, 1957, with the chief complaint of refusal or inability to walk following a minor fall. She had been sickly and slow in growth for about a year. She had been born at term of healthy parents after an uneventful pregnancy, labor, and

**Table II.** Glycogen storage disease: General observations

| *Case* | *Patient* | *Age at diagnosis* | *Age last seen* | *Presenting symptoms* | *Signs of protein deficit* | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Growth and development* | *Musculature* | *Osteoporosis* | *Skin* |
| 1 | V. A. S. | 4 months | 4 years | Coma, convulsions, acidosis | Severely retarded | Very poor | Very marked | Very delicate |
| 2 | D. A. R. | 6 months | 6 months | Slow gain | Retarded | Poor | Very marked | |
| 3 | M. A. L. | 5 months | 12 months | Slow gain, abdominal enlargement | Retarded | Poor | Moderate | |
| 4 | B. C. K. | 4 months | 5 months | Liver enlargement | Retarded | Poor | Mild | |
| 5 | M. C. | 4 months | 5 months | Abdominal mass | Normal | Normal | None | Normal |
| 6 | J. M. | 3 years | 12 years | Liver enlargement | Retarded | Poor | Moderate | Delicate |
| 7 | B. M. | 3 months | 6 years | Hypoglycemia | Retarded | Poor | Moderate | Delicate |

**Table III.** Glycogen storage disease: Hepatomegaly and hepatic function studies

| *Case* | *Hepatomegaly* | *A/G (Gm. %)* | *Prothrombin concentration % control* | *Thymol turbidity (units)* | *Serum lipid (mg. %)* | *Serum cholesterol (mg. %)* |
|---|---|---|---|---|---|---|
| 1 | Marked | 2.6/3.8 | 17 | 8.1 | 1783 | 334 |
| 2 | Marked | 4.4/2.3 | – | 12.6 | 5833 | 286 |
| 3 | Marked | 4.6/2.5 | – | 19.8 | – | – |
| 4 | Marked | 3.5/4.0 | 100 | – | (Milky) | 920 |
| 5 | Marked | – | – | 7.7 | 837 | 286 |
| 6 | Moderate | – | * | – | – | – |
| 7 | Moderate | – | * | – | | – |

*Frequent epistaxis.

**Table IV.** Primary hepatic tumors: General and skeletal status before and following removal of hepatic tumor

| *Case* | *Preoperative status* | | | *Operation* | | *Follow-up status* | | |
|---|---|---|---|---|---|---|---|---|
| | *General* | *Skeletal* | *Date* | *Procedure* | *Diagnosis* | *Date* | *General* | *Skeletal* |
| 8 | Hepatomegaly | Marked osteoporosis | May 22, 1957 | Right lobectomy | Primary benign hepatoma | May 20, 1960 | Thriving | Normal |
| 9 | Hepatomegaly Malnutrition | Marked osteoporosis | July 18, 1958 | Right lobectomy | Primary benign hepatoma | July 22, 1960 | Thriving | Normal |
| 10 | Hepatomegaly | Moderate osteoporosis | Dec. 5, 1955 | Right lobectomy | Primary benign hepatoma | July 15, 1959 | Thriving | Normal |
| 11 | Hepatomegaly | Mild osteoporosis | June 6, 1956 | Right lobectomy | Primary hepatoma: ?malignant | Feb. 15, 1960 | Thriving | – |
| 12 | Hepatomegaly | Moderate osteoporosis | Dec. 13, 1955 | Right lobectomy | Primary benign hepatoma | Mar. 15, 1960 | Thriving | – |
| 13 | Hepatomegaly Repeated URI | Normal | Mar. 7, 1955 | Incomplete resection, right lobe | Primary benign hepatoma: necrosis, bleeding | Mar. 7, 1955 | Died | – |
| 14 | Hepatomegaly | Normal | Oct. 24, 1957 | Left lobectomy | Embryonal carcinoma | Nov. 15, 1957 | Died | – |
| 15 | Hepatomegaly Splenomegaly | Marked osteoporosis | Sept. 10, 1958 | Biopsy right lobe | Embryonal carcinoma inoperable | Sept.23, 1958 | Died | – |
| 16 | Hepatomegaly | Normal | July 14, 1958 | Right lobectomy | Embryonal carcinoma | July 14, 1958 | Died | – |

**Table V.** Hepatic cirrhosis: General observations

| Case | Patient | Sex | Age at onset | Age last seen | Menses | Febrile episode and weakness | Corticosteroid therapy | Present status |
|---|---|---|---|---|---|---|---|---|
| 17 | W. T. | M | 2 | 5 | – | + | None | Active progressive disease |
| 18 | K. S. | M | 2 | 4½ | – | + | On and off | Died: pneumococcal sepsis |
| 19 | S. P. | F | 12 | 14 | 0 | 2+ | 5 months | Improved: going to school |
| 20 | S. S. | F | 11 | 13 | 0 | 2+ | 9 months | Improved: going to school |
| 21 | J. G. | F | 10 | 19 | 0 | 4+ | 6 years, none for 1 year | Symptomatic improvement Recent fracture of femura |
| 22 | L. S. | F | 11 | 12 | 0 | + | 8 months | Slow deterioration |
| 23 | F. W. | F | 7 | 16 | 0 | 3+ | None | Died: hemorrhage, jaundice |
| 24 | J. S. | F | 12 | 14 | 0 | + | 6 weeks | Died: hemorrhage and staphylococcal sepsis |
| 25 | L. S. | F | 14 | 17 | 0 | 2+ | 5 weeks | Died: hemorrhage and coma |
| 26 | S. G. | F | 10½ | 12 | 0 | 2+ | None | Active progressive disease |

**Table VI.** Hepatic cirrhosis: Results of liver function studies

| Case | Albumin | Globulin | Gamma globulin (Gm. %) | Cephalin-cholesterol flocculation | Thymol turbidity (units) | Prothrombin (%) | Alkaline P-tase B.U. | Bilirubin (mg. %) | BSP (%) |
|---|---|---|---|---|---|---|---|---|---|
| 17 | 3.2 (5)* | 2.6 (5) | – | 4+ (1) | 5.0 (5) | 85 (4) | 12.1 (1) | 3.7 (5) | 14.5 (3) |
| 18 | 4.0 (9) | 3.7 (9) | 1.6 (7) | 2+ (1) | 9.6 (2) | 76 (1) | 3.7 (2) | 2.0 (3) | 5.0 (1) |
| 19 | 3.1 (8) | 5.5 (8) | 3.4 (8) | 2+ (2) | 6.8 (2) | 90 (1) | 2.2 (1) | 0.3 (1) | 0.0 (1) |
| 20 | 2.6 (5) | 6.5 (5) | 7.4 (2) | 3+ (6) | 14.5 (7) | 69 (3) | 3.4 (3) | 1.8 (1) | 15.2 (1) |
| 21 | 1.7 (11) | 4.4 (11) | 2.2 (2) | 3+ (8) | 12.5 (8) | 75 (3) | 17.5 (5) | 1.2 (2) | 0.0 (1) |
| 22 | 2.1 (10) | 5.4 (10) | 6.0 (3) | 4+ (7) | 11.7 (10) | 33 (15) | 15.2 (1) | 10.6 (4) | 36.1 (4) |
| 23 | 2.5 (5) | 6.6 (5) | – | 4+ (2) | 18.9 (6) | 22 (4) | 24.0 (2) | 7.8 (4) | 38.0 (2) |
| 24 | 2.9 (2) | 3.6 (2) | 2.2 (1) | 4+ (2) | 5.5 (2) | 55 (3) | 13.7 (2) | 1.4 (3) | 31.8 (2) |
| 25 | 2.7 (9) | 4.6 (9) | | 4+ (5) | 16.2 (4) | 57 (3) | 13.9 (6) | 3.9 (7) | – |
| 26 | 2.6 (3) | 9.0 (3) | 7.0 (1) | 4+ (2) | 17.2 (2) | 51 (7) | 4.1 (3) | 12.8 (4) | – |

*Numerical figure in parentheses represents number of determinations from which average result is calculated.

**Table VII.** Hepatic cirrhosis: Osteoporosis and nutritional status*

| Case | Age | Osteoporosis | Weight (lb.) | Height (inches) | Nutritional status | Remarks |
|---|---|---|---|---|---|---|
| 17 | 5 | Moderate | 25 (1½ years)† | 35½ (2 years)† | Very poor | No steroid therapy |
| 18 | 4½ | Moderate | 35 (3½ years)† | 39 (4 years)† | Very poor | No change with steroid therapy |
| 19 | 14 | Mild | 78 (108)‡ | 59 | Poor | Rapid gain to 106 pounds in 6 months with steroid therapy |
| 20 | 13 | Moderate | 79 (98)‡ | 62 | Poor | Rapid gain to 114 pounds in 5 months, with steroid therapy |
| 21 | 19 | Marked | 56 (8 years)† | 52½ (9 years)† | Extremely poor | Occurred before steroid therapy |
| 22 | 12 | None | 153 | 65 | Normal | Cushingoid with steroid therapy |
| 23 | 16 | Moderate | 105 | 57 | Poor | No change with steroid therapy |
| 24 | 14 | None | 130 | 65 | Normal | |
| 25 | 17 | None | 114 | 65 | Normal | |
| 26 | 12 | Mild | 78 | 58 | Normal | Recent loss of weight |

*Observations prior to institution of steroid therapy.
†Age with 50th percentile weight and height corresponding with those of the patient.
‡Normal weight for 50th percentile at patient's age.

delivery. The birth weight was 6⅓ pounds. The dietary history was satisfactory. The developmental milestones up to the age of 18 months were within expected ranges. She weighed 19½ pounds then, but gained only 1 pound in the next 12 months. There was no history of gastrointestinal disorder, urinary tract infection or other serious childhood diseases.

Physical examination showed a poorly developed, undernourished, pale, irritable, and sickly looking child. The height of 32 inches and weight of 20½ pounds were considerably below normal standards and corresponded with the 50th percentile for the age of 18 and 12 months, respectively. The hair was thin and lusterless, nails soft and poorly developed. The skin was delicate and the musculature small and weak. The head and chest organs were essentially negative. The abdomen was roundly protuberant. The liver was moderately enlarged, firm, nontender, smooth, round edged, and extended 6 cm. below the right costal margin to the iliac crest. The spleen and kidney were not palpable. The neurological findings were normal.

**Radiographic findings.** A large hepatic mass and severe generalized osteoporosis were demonstrated before the operation (Figs. 6, *A* and 7, *A*).

**Laboratory studies.** The serum calcium, phosphorus, and alkaline phosphatase were normal. The urinary excretion of calcium and phosphate was decreased. The serum protein concentration and other indices of liver function were within normal ranges. There was no serious anemia. The urinalysis was negative. A bone biopsy showed no evidence of increased osteoblastic or osteoclastic activity, and the histologic findings were consistent with osteoporosis. The glucagon and epinephrine tests showed poor response before operation, normal response after the removal of the tumor (Fig. 8).

**Surgical treatment and postoperative follow-up.** Exploratory laparotomy was carried out May 21, 1957, and a large tumor of the right lobe of the liver was found. Right hepatolobectomy was performed the next day. The pathologic diagnosis was benign hepatoma almost completely replacing the right lobe of the liver (Fig. 9*A*). Microscopically the tumor cells were laden with

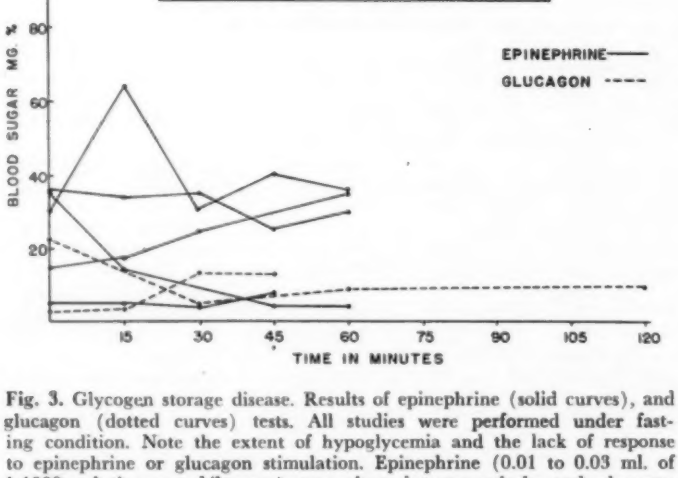



Fig. 3. Glycogen storage disease. Results of epinephrine (solid curves), and glucagon (dotted curves) tests. All studies were performed under fasting condition. Note the extent of hypoglycemia and the lack of response to epinephrine or glucagon stimulation. Epinephrine (0.01 to 0.03 ml. of 1:1000 solution per kilogram) was given intramuscularly and glucagon (4 mg. per kilogram) intravenously at zero time after fasting blood sample was drawn.

glycogen (Fig. 9*B*). Histologically this is quite similar to glycogen storage disease (Fig. 4). The immediate postoperative course was stormy with many complications. But the patient recovered and went home improved in July, 1957. She has been followed regularly in the outpatient clinic. The osteoporosis gradually disappeared (Figs. 6, *B* and 7, *B*), and the general condition improved. When last seen in May, 1960, she stood 42 inches tall and weighed 40 pounds, both measurements were normal for her age. The progress of the growth and development is shown in Fig. 10.

The observations on the entire group of children with primary hepatic tumors are presented below.

*General observations.* There were 6 girls and 3 boys in the series. Their ages ranged from 12 to 57 months with a mean of 28 months at the time of diagnosis. Massive hepatomegaly was present in all. Six patients were asymptomatic; 4 were described as healthy, happy, active, and alert. The hepatic mass was discovered incidentally by the pediatrician during routine examination in 3 and by the parents because of unusual prominence of the abdomen in 3 other children. One child was seen for repeated upper respiratory infection and another for inability to walk; in both instances the hepatic tumor was found incidentally. Only one child had serious symptoms clearly referable to the liver disease.

*Osteoporosis.* Generalized osteoporosis was demonstrated in 6 of the 9 children. Of these 3 showed improvement following resection of the tumor (Fig. 11); 2 are living in good health but have had no follow-up x-ray examination; and 1 died shortly after operation. These observations are summarized in Table IV.

*Laboratory findings.* Some lowering of hemoglobin concentration was found quite frequently, the values ranged from 5.5 to 13.0 Gm. per cent with a mean of 10.0 Gm. per cent.

The liver function tests only rarely showed decidedly abnormal values. In one patient with extensive necrotic embryonal carcinoma

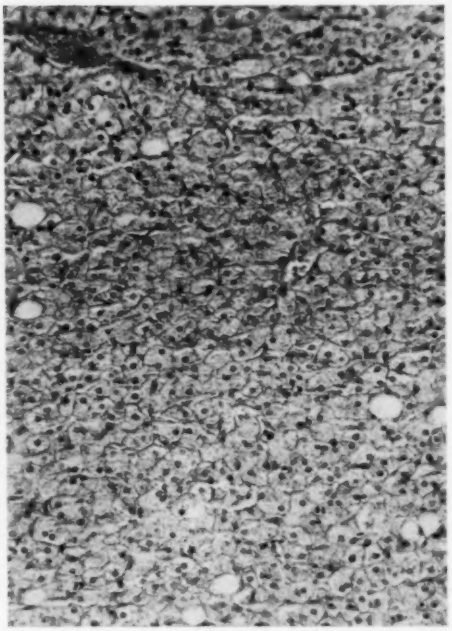
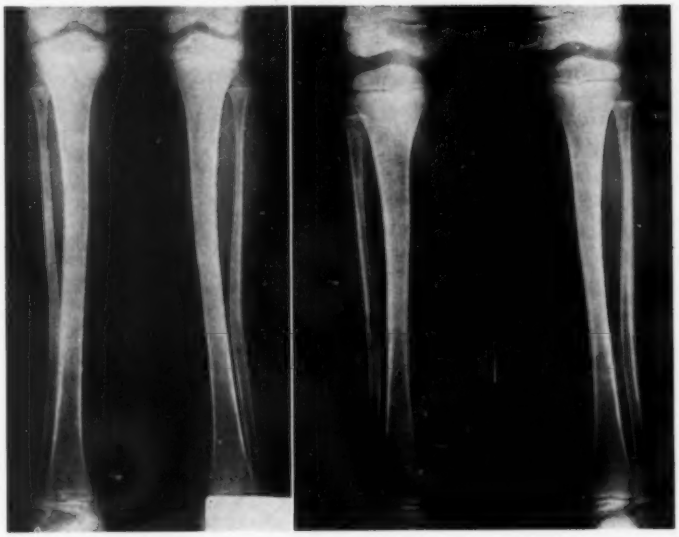


**Fig. 4.** Case 1. Liver biopsy. Note large liver cells with bundant clear cytoplasm filled with glycogen. (Hematoxylin and eosin. Original magnification ×130.)

completely destroying the entire right lobe of the liver, there was elevation of serum bilirubin (1.6 to 5.0 mg. per cent), increase in thymol turbidity (14 to 19 units), positive cephalin-cholesterol flocculation, and severe anemia (5.5 Gm. per cent). The total serum protein and the A/G ratio were within normal limits in 4 patients, and the prothrombin and alkaline phosphatase activities were not remarkably altered in 3 patients in whom these studies had been done.

It would appear that despite the destruction and replacement of a considerable portion of normal liver by hepatoma or carcinoma, the functional indices tested were for the most part not significantly abnormal. These observations are indicative of the remarkable functional reserve of the liver. It seems conceivable, however, that the manifest normalcy might have been made possible only at the expense of other organs, such as bone and muscle which sustained atrophic changes.



*A* *B*

**Fig. 5.** *(A)* Case 6, aged 12 years, and *(B)* Case 7, aged 6 years. Moderate osteoporosis with slight bowing of tibia and fibula. Note transverse lines of growth disturbance.

## III. HEPATIC CIRRHOSIS

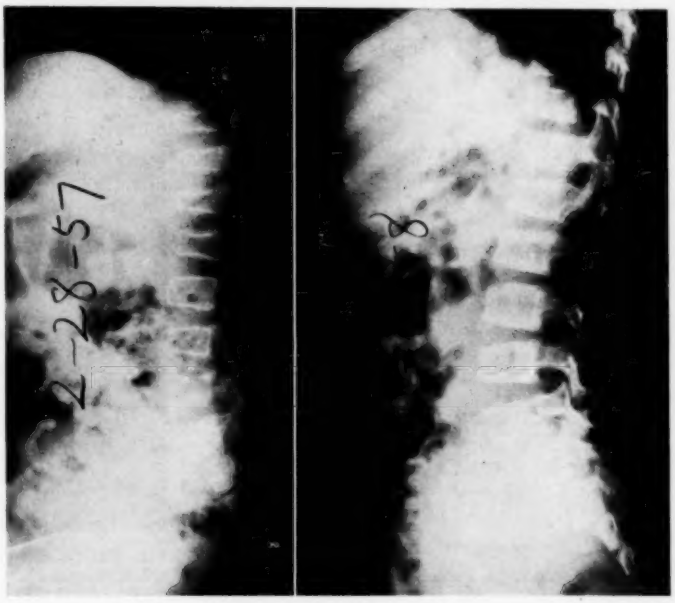
In chronic hepatitis with or without postnecrotic cirrhosis, serious impairment of hepatocellular function and disturbance of protein metabolism are apt to occur. Although growth retardation, muscle atrophy, anemia, hypoproteinemia, and other deficiency symptoms are well known in chronic hepatic cirrhosis,[3, 16, 17] osseous lesions, their nature, and frequency are less well appreciated and rarely documented. This is especially true of osteoporosis in children with chronic hepatitis and postnecrotic scarring.[6]

In our hospitals we have seen 10 children with chronic hepatitis, of whom 9 had postnecrotic cirrhosis. In all but one (Case 21) of these patients the diagnosis was established by microscopic examination. Seven of these children showed osteoporosis and other manifestations of growth disturbance.

**General observations.** There were 2 boys and 8 girls in the series. At the time of onset, each boy was 2 years and the girls from 7 to 14 years of age. The onset was insidious in all except Case 24, and the duration of the disease up to the time of last follow-up

*A* *B*

**Fig. 6.** Case 8. *A*, April, 1957, severe osteoporosis before hepatolobectomy for primary hepatoma. *B*, May, 1960, improvement of osteoporosis following complete removal of tumor.




*A* *B*

**Fig. 7.** Case 8. *A*, February, 1957, severe osteoporosis of vertebral column before hepatolobectomy. *B*, November, 1958, improvement of osteoporosis following removal of hepatoma.

varied from 1 to 9 years. One boy (Case 18) has died of fulminating pneumococcal sepsis at 4½ years of age, 3 girls (Cases 23, 24, and 25) have died of massive hemorrhage and hepatic insufficiency after 9, 2, and 3 years of illness, respectively. All patients had febrile episodes. None of the girls had menarche. Several patients received corticosteroid therapy with varying degrees of symptomatic improvement. This information is shown in Table V.

**Liver biopsy.** Biopsy of the liver was carried out in 9 patients; 8 of these showed postnecrotic scarring with varying degrees of acute and/or chronic hepatic inflammation. Plasma cell infiltration varied in intensity from case to case. The portal pressure was increased (160 to 420 mm. water) in 5 cases in whom it was directly measured at laparotomy for liver biopsy. In Case 17, normal histology was found when the liver biopsy was obtained shortly after the onset of the disease; but chronic hepatitis was evident at postmortem examination 2½ years later. In Case 21 a liver biopsy was not obtained; however, the diagnosis of severe hepatic cirrhosis was unquestioned on the basis of clinical and laboratory findings.

**Symptoms and signs.** Hepatomegaly and splenomegaly of varying degrees were quite constant findings. Clinical icterus varied in intensity in 8 and was absent in 2 patients; the serum bilirubin concentrations are shown in Table VI. Ascites was present in 5 patients. Marked esophageal varicosity was demonstrable in 2 patients; both had massive bleeding. Of 3 patients in whom the demonstration of esophageal varices was inconclusive, 2 had severe hemorrhages. Moderate to severe anemia was observed in all 10 patients. Blood loss from esophageal varices and from repeated epistaxis were responsible for the anemia in 7 and a hemolytic process in 1 other patient.

**Liver function studies.** Moderate to marked decrease in serum albumin with lowered or reversed A/G ratio was found in all patients. The concentration of gamma

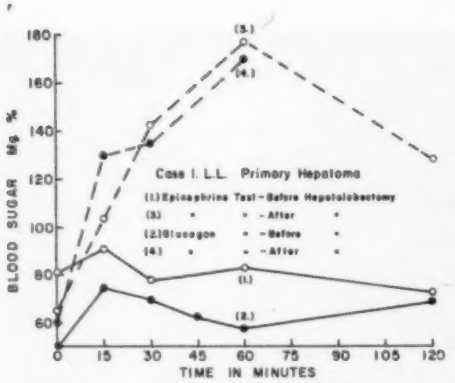

BLOOD SUGAR Mg %
TIME IN MINUTES
Case I. L.L. Primary Hepatoma
(1) Epinephrine Test - Before Hepatolobectomy
(3) " " - After "
(2) Glucagon " - Before "
(4) " " - After "

**Fig. 8.** Case 8. Response to epinephrine and glucogen tests before and after removal of primary hepatoma. Poor preoperative response to both tests indicative of glucose-6-phosphatase deficiency in glycogen-laden tumor cells (see Fig. 9).

globulin was consistently increased, exceeding 7 Gm. per cent in 2 patients (Cases 20 and 26). Positive cephalin-cholesterol flocculation tests were observed in all but 1, and an elevated thymol turbidity in 7 cases. The prothrombin activity was decreased in 6 patients; as a rule the response to vitamin K therapy was poor. The serum alkaline phosphatase activity was slightly above normal in 3, markedly elevated in 1, and within normal limits in 6 patients. The serum bilirubin concentration was below 1 mg. per cent in only 1 patient, and above 10 mg. per cent in 2 cases. The BSP test showed abnormal retention in 4 of 7 patients so studied. On the whole these studies revealed moderate to severe impairment of hepatocellular functions in all 10 patients of the series (Table VI).

**Osteoporosis and nutritional status.** Osteoporosis was present in 7 of the 10 patients (Table VII). It was considered severe in 1, moderate in 4, and mild in 2 cases (Figs. 12 and 13).

It is significant that at least 1 patient (Case 19) showed improvement of the osteoporosis (Fig. 13) which accompanied improvement of the liver function and the general condition as evidenced by increase in weight, strength, and well-being following judicious use of corticosteroid therapy.

The serum calcium and inorganic phosphorus concentrations were within normal range in 5 patients including 3 cases with osteoporosis and were not determined in the

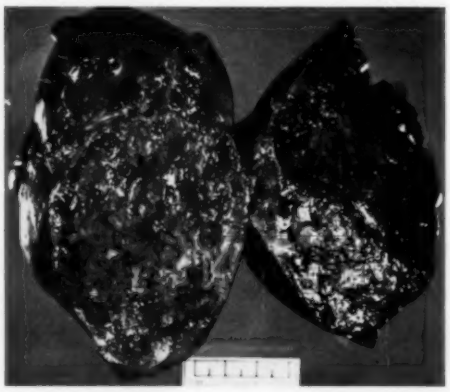


**Fig. 9*A*.** Case 8. Gross surgical specimen of primary hepatoma. The well-encapsulated tumor, 12.5 by 11.0 by 6.0 cm. in size, weighing over 800 Gm., nearly replaced the entire right lobe.

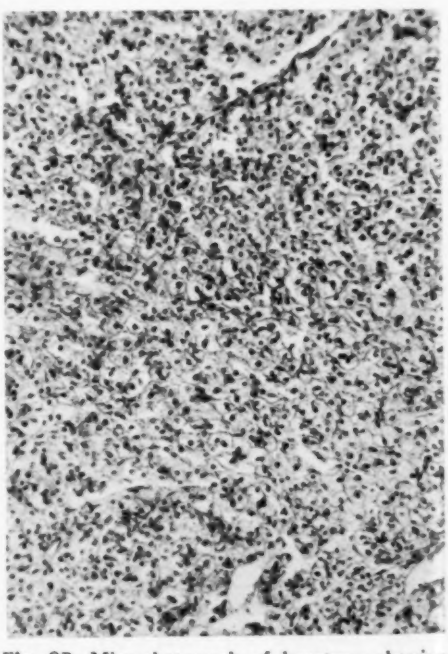


**Fig. 9*B*.** Microphotograph of hepatoma showing tumor cells ballooned with glycogen. Note similarity in comparison with glycogen storage disease shown in Fig. 4.

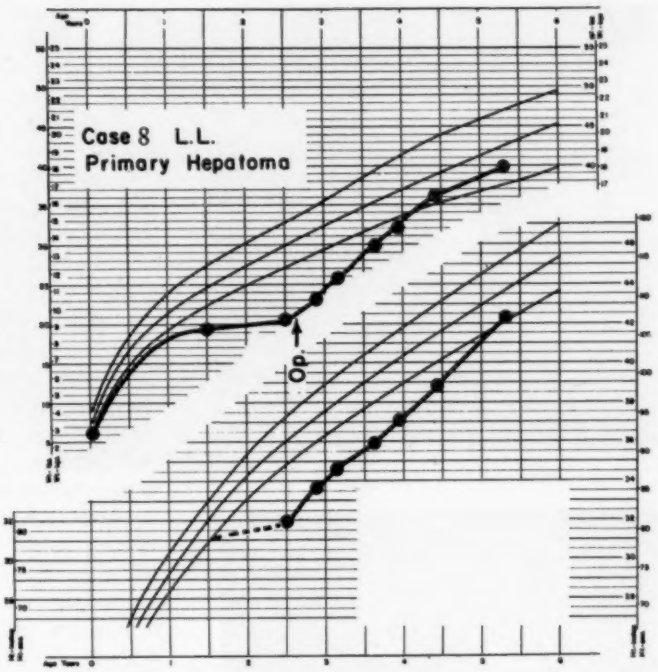



**Fig. 10.** Case 8. Complete arrest of growth for a year or more prior to surgical treatment and rapid recovery after removal of hepatoma. Note parallel changes in bones shown in Figs. 6 and 7.

other 5 patients. The serum alkaline phosphatase activity was increased in 4 patients. This may be related to the liver disease rather than to bone change.

The general nutritional status was very poor in 3 patients, poor in 5, and relatively normal in 2. This was reflected in the stunting of growth in stature and weight of these children (Figs. 14 and 15). These manifestations were most marked in Case 21, whose growth and development were completely arrested with the onset of the long illness; at the present age of 19 years, she has the height of a 9-year-old and the body weight of an 8-year-old (Fig. 14). The bones are extremely osteoporotic and the muscles markedly atrophied (Fig. 12, *B*). Recently she had a minor fall and suffered pathologic fractures of both femurs (Fig. 12, *B*). All of the growth disturbances had apparently developed long before she was given sustained corticosteroid therapy.

## DISCUSSION

From the data presented it is apparent that the high incidence of osteoporosis in 3 different types of liver diseases suggests a common explanation. Normal growth of bone requires an adequate supply of protein and balanced activities of the endocrine glands. In the absence of overt endocrine disorder, a deficit of protein seems a logical etiological factor, which would also explain the frequent occurrence of muscular atrophy and growth retardation in these children.

One question which immediately arises is the lack of commonly accepted evidence of protein deficiency, such as hypoproteinemia, anemia, edema, etc., in most of the patients except those with cirrhosis.

We envisage a distinction between the state of advanced protein *deficiency,* in which hypoproteinemia is a cardinal sign, and the state of relative protein *deficit,* in

*A*

*B*

**Fig. 11.** Case 9. Primary benign hepatoma. *A*, July, 1958, marked osteoporosis before hepatolobectomy. *B*, January, 1960, improvement of osteoporosis after resection of tumor.

which the serum protein concentration may be normal but the growth of certain tissues may be retarded. With the assumption that atrophic changes of bone and muscle and retardation of growth are manifestations of a systemic deficit of protein, 2 questions remain to be answered. First, what are the possible pathophysiologic mechanisms responsible for the genesis of a protein deficit in the liver diseases under discussion? This will be discussed below. Second, why are the usual signs of protein deficiency not found in many of our patients? This will be discussed in a subsequent paper.

The importance of the liver in many phases of metabolism is well established. The liver is the major organ which synthesizes plasma proteins,[18] its proteins are readily mobilized and available to other organs through the agency of the circulating plasma.[19] It is also important in the intermediary metabolism of carbohydrate and fat.[20, 21] Furthermore, while many hormones act upon the liver cells and regulate their enzymatic activities, they are also inactivated in the hepatic cells.[22] In these multiple roles the liver participates in the dynamic flux of the metabolic pool. It should not be surprising, therefore, that severe liver diseases with serious hepatic dysfunction will have far-reaching effects on metabolic and physiologic processes, and that a *relative* or absolute protein deficit may develop. As a result of such shortage other organs may be deprived of their protein supply, or their protein stores may be mobilized,[19] and osteoporosis and other atrophic changes may therefrom eventuate.

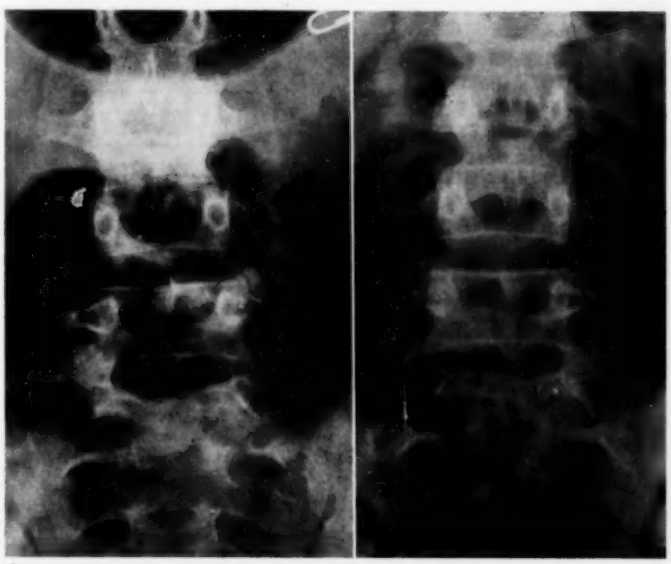
The pathogenesis of protein deficit in each type of liver disease may now be considered more specifically.

**I. Glycogen storage disease.** In von Gierke's disease the fundamental abnormality is a deficiency or virtual absence of hepatic (and renal) glucose-6-phosphatase.[23] The function of glucose-6-phosphatase is to catalyze the hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate—an all important reaction in the maintenance of blood sugar concentration through hepatic glycogenolysis and gluconeogenesis.

Glucose-6-phosphate is an important intermediate of carbohydrate metabolism. By way of the Embden-Meyerhof scheme of glycolysis and the Krebs cycle of oxidative reactions it is also in dynamic equilibrium with protein and fat metabolism. These relationships provide the biochemical basis for a host of secondary disorders consequent upon abnormal metabolism of glucose-6-

*A* *B*

**Fig. 12.** Case 21. Female patient with chronic hepatitis and severe postnecrotic cirrhosis since 9 years of age in 1951. *A*, Severe osteporosis, 1954. *B*, More severe osteoporosis with pathologic fractures, 1960. Also note marked muscle atrophy and extreme emaciation (see Fig. 14).



*A* *B*

**Fig. 13.** Case 19. Female patient, aged 12 years, with chronic hepatitis and postnecrotic cirrhosis of 2 years' duration. *A*, mild but definite osteoporosis of lumbar vertebrae before corticosteroid therapy. *B*, improvement of osteoporosis with appreciable increase in thickness of cortical plates of corresponding vertebrae after 5 months of corticosteroid treatment. Patient also showed improvement of nutritional status and general well-being.

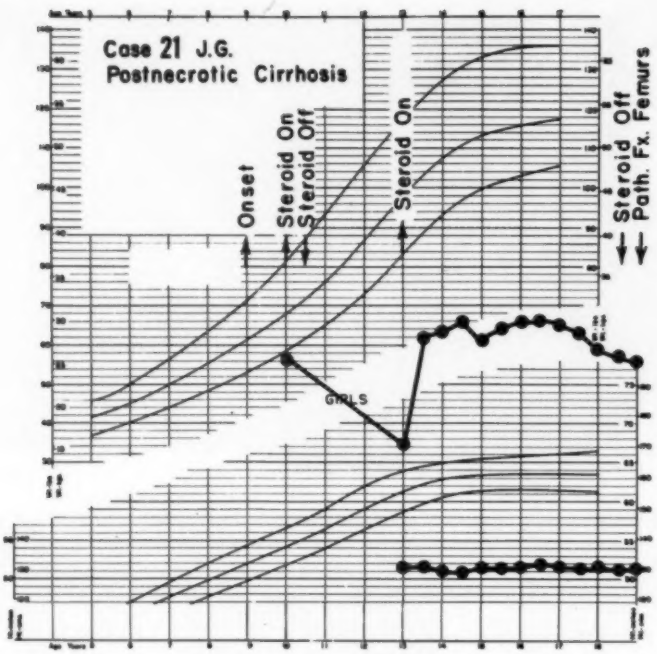



**Fig. 14.** Case 21. Protracted (10 years) course of postnecrotic cirrhosis with complete arrest of growth and development since onset of disease (see Fig. 12 for bone changes).

phosphate in von Gierke's disease, which is primarily a disturbance of glucose and glycogen metabolism. It has been estimated[21] that under normal conditions 55 per cent of the glucose-6-phosphate pool in the liver is hydrolyzed to glucose and inorganic phosphate which are returned to the blood. This is the only mechanism by which glucose is produced in the body from hepatic glycogen and from other sources (gluconeogenesis). Glucose-6-phosphate has 3 other metabolic pathways including the formation of glycogen via glucose-1-phosphate. The rate of these reactions may be increased on a pro rata basis when hydrolysis is blocked on account of glucose-6-phosphatase deficiency.

The absence or deficiency of glucose-6-phosphatase, therefore, would result in 2 primary metabolic defects: under production of glucose and overproduction of glycogen giving rise to a propensity to hypoglycemia and abnormal accumulation of glycogen storage proportional to the degree of enzyme deficit. These in turn would lead to a number of secondary metabolic disturbances and to structural and functional abnormalities of the liver (and kidney) with grave and fatal clinical manifestations. The chain reactions are comparable to those of hunger diabetes.[14] First, the want of carbohydrate fuel for energy metabolism would stimulate the catabolism of protein and of fat leading to protein deficit, hyperlipemia, acidosis, dehydration, and electrolyte imbalance. Second, the damage to hepatic function would further impair the body's capacity to cope with the adverse protein economy. In addition hormonal disturbances secondary to stress and reduction of food intake due to anorexia and vomiting would further aggravate the situation (Fig. 16). Balance study has shown that as much as 3 to 4 Gm. of protein per day, or more than 1 kg. of protein per year, were lost to a 5½-

year-old boy with moderately severe glycogen storage disease.[14] It is obvious that in the long run this order of protein deficit will not be sustained without depleting the body's protein reserve and leading to osteoporosis, muscle, and skin atrophy, and growth retardation.

**II. Primary hepatic tumors.** In the 2 reports in which 2 well-studied cases were presented and a third briefly mentioned, Hansen, Zeigler, and McQuarrie[5] and Roberts and Sullivan[6] made extensive studies of the lipid and calcium metabolism. They were impressed with the findings of hyperlipemia and hypercholesterolemia in these children. They speculated about the possibility of a missing liver factor that might be responsible for the disturbed lipid metabolism and the inability of the bone to retain calcium and phosphorus. Retarded growth and muscle wasting were also conspicuous in their cases as in ours. The possibility of a protein deficit being the common denominator has not received serious consideration.

In our patients with hepatic tumors there were no data on serum lipid or cholesterol concentrations. However, hyperlipemia and

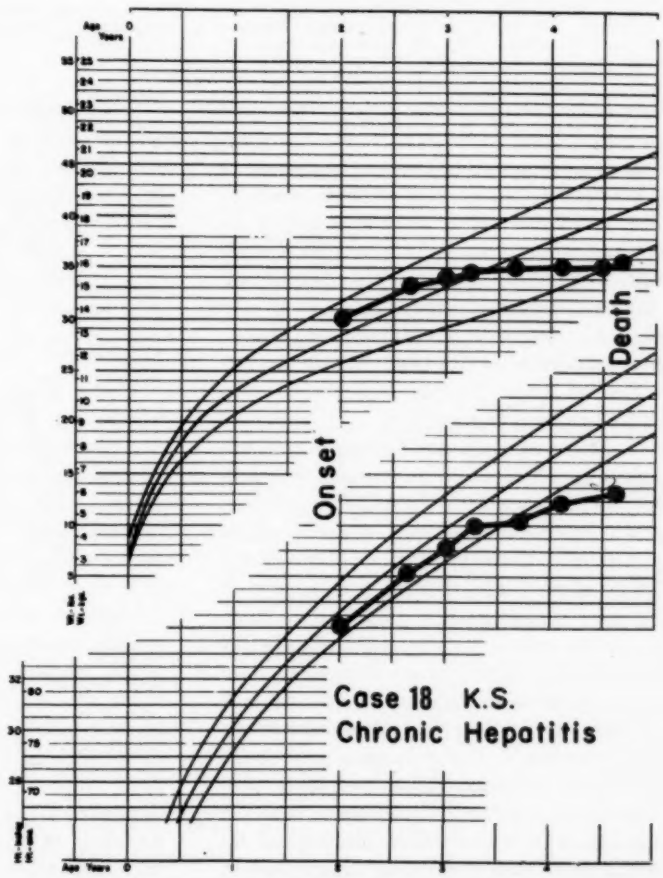



**Fig. 15.** Case 18. Boy with chronic hepatitis, onset at 2 years and death at 4½ years of age. Note retardation of growth. The bones were moderately osteoporotic.

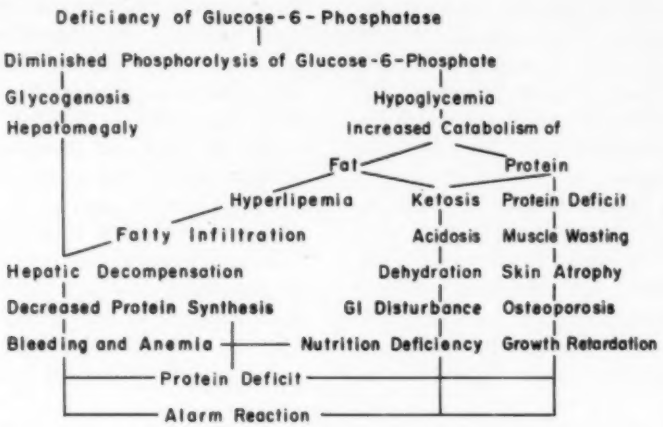



**Fig. 16.** Pathologic physiology of glycogen storage disease. Note pathogenesis of protein deficit, osteoporosis, emaciation, growth retardation.

hypercholesterolemia are generally believed to be common findings in severe liver disease of many causes. They were present in a majority of our patients with von Gierke's disease (Table III). They are due to increased utilization of fat and may cause fatty infiltration of the liver leading to additional hepatic damage, and thus secondarily contribute to diminished hepatic protein synthesis (Fig. 16).

Several other possible causes of protein deficiency may be suggested:

1. Microscopically the hepatoma cells are rich in glycogen while the normal liver cells are not. In Case 8 the response to glucagon and epinephrine tests were negative before and positive after the tumor was removed. These observations indicate a deficiency of glucose-6-phosphatase in the glycogen-laden hepatoma cells,[25-27] a situation metabolically similar to glycogen storage disease. In most of our patients, from one third to one half or more of the liver was destroyed and replaced by tumor. If the glycogen store in the hepatoma were unavailable for glucose production, a tendency to hypoglycemia[28-30] and increased utilization of protein and fat would result with consequent protein deficit, hyperlipemia and other abnormalities much the same as in von Gierke's disease (Fig. 16).

2. In addition, when a large portion of normal liver is lost, functional impairment will become inevitable. Although this may be compensated and inapparent, hepatic protein synthesis may be adversely affected and a supply shortage may develop.

3. Furthermore, the growth of the tumor imposes an additional demand for protein, aggravating the already precarious economy.

Under these circumstances of increased catabolism, decreased synthesis, and abnormal requirement, a deficit of protein cannot be avoided for long, and in time the large protein stores of the body will bear the brunt of deprivation. Indeed, the total net balance of protein economy may become so unfavorable that emaciation of muscle and skin, atrophy of bone and retardation of growth become inevitable.

**III. Hepatic cirrhosis.** The cirrhotic patients showed the most severe impairment of liver function in comparison with the patients with glycogen storage disease or hepatic tumors. All but one patient showed hypoalbuminemia and reversed A/G ratio; one half of the patients had ascites. For the pathogenesis of this advanced degree of protein deficit a number of possible causes may be responsible. These are as follows:

1. Decreased synthesis of protein as re-

flected by hypoalbuminemia and hypoprothrombinemia.

2. Increased demand for increased production of antibodies as evidenced by hypergammaglobulinemia.

3. Increased destruction of tissue proteins due to persistent inflammation.

4. Increased loss of protein due to hemorrhage.

5. Increased demand of proteins for repair of destroyed tissues and regeneration of lost red cells.

6. Nutritional deficiency due to diminished intake, disturbed digestion, and absorption secondary to severe liver disease.

7. Hormonal disturbances, such as possible alarm reaction, suppression of gonadal function, and long-term corticosteroid therapy.

The relative importance of each of these factors may vary in individual patients, but the total effect on body protein economy with resultant osteoporosis, muscle wasting, and growth failure is similar in all instances. Many of our patients have received corticosteroid therapy. However, for the most part they developed osteoporosis and other symptoms of protein deficit before they were placed on long-term steroid medication. Furthermore, those who responded favorably to steroid therapy showed no additional deleterious effect on their protein economy, rather, they were improved in general well-being and in strength. In addition, osteoporosis and growth failure occurred just as frequently in those children who received no steroid treatment.

## SUMMARY

1. Of 7 children with glycogen storage disease, 9 with primary hepatic tumors, and 10 with hepatic cirrhosis, approximately two thirds of them had osteoporosis, and many also had muscle atrophy and growth retardation.

2. One child with benign hepatoma showed dramatic improvement after the tumor was removed.

3. These observations suggest that a systemic deficit of protein may be an important etiological factor of osteoporosis in liver diseases.

4. The pathogenesis of protein deficit in each type of liver disease has been considered.

## REFERENCES

1. Sherlock, S.: Diseases of the Liver and Biliary System, Springeld, Ill., 1955, Charles C Thomas, Publisher, pp. 377-379.
2. Follis, R. H., Jr.: Deficiency Disease, Springfield, Ill., 1957, Charles C Thomas, Publisher, pp. 86.
3. Amberg, S., and Logan, G. B.: Diseases of Liver and Biliary Tract, in McQuarrie, I., editor: Brennemann's Practice of Pediatrics, Hagerstown, 1948, W. F. Prior Co., Inc., vol. 3, pp. 70-72.
4. Beumer, H.: Ueber den Cholesterinstoffwechsel bei der Glykogenspeicherkrankheit, München. med. Wchnschr. **84:** 1007, 1937.
5. Hansen, A. E., Zeigler, M. R., and McQuarrie, I.: Disturbance of Osseous and Lipid Metabolism in a Child With Primary Carcinoma of the Liver, J. Pediat. **17:** 9, 1940.
6. Roberts, M. H., and Sullivan, C.: Influence of the Liver on Bone Metabolism. Report of Two Cases, J. A. M. A. **159:** 1002, 1955.
7. Cocchi, von U.: Hepatogene Osteoporosen, Radiol. Clin. **20:** 362, 1951.
8. von Gierke, E.: Hepato-Nephromegalia glykogenica (Glykogenspeicherkrankheit der Leber und Nieren), Beitr. z. path. Anat. allg. Path. **82:** 497, 1929.
9. Mason, H. H., and Anderson, D. H.: Glycogen Disease, Am. J. Dis. Child. **61:** 795, 1941.
10. Mason, H. H., and Anderson, D. H.: Glycogen Disease of the Liver (von Gierke's Disease) With Hepatomata, Pediatrics **16:** 785, 1955.
11. Abramson, H., and Kurtz, L. D.: Familial Glycogen Disease: Report of Four Cases of Hepatic Form of Disease in Siblings of One Family, Am. J. Dis. Child. **77:** 510, 1946.
12. Schulman, J. L., and Saturen, P.: Glycogen Storage Disease of the Liver. I. Clinical Studies During Early Neonatal Period, Pediatrics **14:** 632, 1954.
13. Bridge, E. M.: Glycogen Storage Disease, in McQuarrie, I., editor: Brennemann's Practice of Pediatrics, Hagerstown, 1948, W. F. Prior Company, Inc., vol. 3, chap. 24A, pp. 1-12.
14. Bridge, E. M., and Holt, L. E.: Glycogen Storage Disease: Observations on the Pathologic Physiology of 2 Cases of the Hepatic Form of the Disease, J. Pediat. **27:** 299, 1945.
15. Edmondson, H. A.: Differential Diagnosis of Tumors and Tumor-Like Lesions of Liver in Infancy and Childhood, A. M. A. J. Dis. Child. **91:** 168, 1956.

16. Follis, R. H., Jr.: Deficiency Disease, Springfield, Ill., 1957, Charles C Thomas, Publisher, pp. 86-89 and 343.
17. Sherlock, S.: Diseases of the Liver and Biliary System, Springfield, Ill., 1955, Charles C Thomas, Publisher, pp. 92-138.
18. Anker, H. S.: The Biosynthesis of Plasma Proteins, in Putnam, F. W., editor: The Plasma Proteins, New York, 1960, Academic Press, Inc., vol. 11, pp. 288.
19. Whipple, G. H.: The Dynamic Equilibrium of Body Proteins, Springfield, Ill., 1956, Charles C Thomas, Publisher.
20. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Interpretation, vol. 1, Baltimore, 1946, Williams & Wilkins Co., pp. 422-438.
21. White, A., Handler, P., Smith, E. L., and Stetten, DeW., Jr.: Principles of Biochemistry, New York, 1954, McGraw-Hill Book Company, Inc., pp. 858-861.
22. White, A.: The Interaction of Enzymes and Hormones, Pediatrics **26:** 476, 1960.
23. Cori, G. T., and Cori, C. F.: Glucose-6-Phosphatase of the Liver in Glycogen Storage Disease, J. Biol. Chem. **199:** 661, 1952.
24. Ashmore, J., and Weber, G.: The Role of Glucose-6-Phosphatase in the Regulation of Carbohydrate Metabolism, in Harris, R. S., Martin, G. F., and Thimann, K. V., editors: Vitamins and Hormones, New York, 1959, Academic Press, Inc., vol. 17, pp. 91-132.
25. Weber, G., and Cantero, A.: Glucose-6-Phosphatase Utilization in Hepatoma, Regenerating and New-Born Rat Liver, and in the Liver of Fed and Fasting Normal Rats, Cancer Res. **17:** 995, 1957.
26. Weber, G., and Cantero, A.: Glucose-6-Phosphatase Activity in Normal Precancerous and Neoplastic Tissues, Cancer Res. **15:** 105, 1955.
27. Harris, R. C., and Olms, C.: Liver and Kidney Glucose-6-Phosphatase Activity in Children With Normal and Diseased Organs, J. Clin. Invest. **33:** 1204, 1954.
28. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated With Primary Liver Cell Carcinoma, Arch. Int. Med. **44:** 700, 1929.
29. Crawford, W. H.: Hypoglycemia With Coma in a Case of Primary Carcinoma of the Liver, Am. J. Med. Sc. **181:** 496, 1931.
30. Beers, D. N., and Norton, J. J.: Primary Carcinoma of the Liver With Hypoglycemia, Am. J. Cancer **24:** 51, 1935.

# *Liver diseases and osteoporosis in children*

## *II. Etiological considerations*

**Ching Tseng Teng, M.D.,* C. William Daeschner, Jr., M.D.,**

**Edward B. Singleton, M.D., and Harvey S. Rosenberg, M.D.**

HOUSTON, TEXAS

THE many causes of osteoporosis, which have been explored by Albright and Reifenstein,[1] have continued to be a subject of interest. In a recent symposium, mainly on senile osteoporosis and Cushing's syndrome, a number of hypotheses were advocated.[2-6] Of these some were familiar, others were radically new; none seemed wholly acceptable to all the participants of the panel. It appears that the antiosteoporosis factor[3] is yet to be demonstrated, the calcium deficiency theory[4] has received little support, and disuse atrophy[5] is of relatively minor importance in the majority of patients. The more conventional concepts of cellular activity[2] and hormonal imbalance[6] still appear to have the most merit.

In addition, the importance of osteogenic cellular differentiation in response to various stimuli has been stressed,[7] and in this connection the tangled interrelationships between hormonal action, metabolic substrates, and cellular or enzymatic activities should deserve consideration.[8, 9]

In this paper we propose to consider the hypothesis that osteoporosis in liver diseases may develop as a compensatory reaction to a systemic protein deficit as a result of hepatic dysfunction.

### OSTEOPOROSIS AND PROTEIN DEFICIT

In children with liver diseases of divergent etiology presented in the preceding paper[10] a high incidence of osteoporosis, muscle wasting, skin atrophy, and growth failure was observed. The findings suggested that deficit of protein might be a significantly common factor, although marked hypoalbuminemia and hypoprothrombinemia were found only in the cirrhotic children. The prompt disappearance of osteoporosis and resumption of growth following improvement or eradication of the liver disease in several instances seem to lend support to the thesis. It would appear that manifest or occult hepatic insufficiency was an important factor in the pathogenesis of a protein deficit in these patients. The possible mechanisms have already been discussed in some detail in each type of liver disease.[10]

*From the Departments of Radiology, Pediatrics, and Pathology, Texas Children's Hospital, and Baylor University College of Medicine, Houston, Texas.*

**Address, Texas Children's Hospital, Houston 25, Texas.*

**Table I.** Causes of protein deficit

| |
|---|
| *I. Insufficient intake* |
| 1. Dietary deficiency |
| 2. Gastrointestinal disorders |
| *II. Diminished synthesis* |
| 1. Liver diseases with hepatic insufficiency |
| 2. Endocrine disorders |
| *III. Increased requirement* |
| 1. Pregnancy, lactation, etc |
| 2. Neoplasia |
| 3. Inflammatory diseases |
| *IV. Increased breakdown and abnormal loss* |
| 1. Endocrine disorders |
| 2. Proteinuria |
| 3. Serous effusions requiring drainage |
| 4. Vomiting, diarrhea, etc. |
| 5. Hemorrhage |

It is interesting to note that atrophic changes of muscle and bone also occur in endocrine disorders and in starvation or malnutrition.[11, 12] It seems obvious that osteoporosis is not a specific manifestation of a single disease; rather it may represent a nonspecific expression of a protein deficit caused by many conditions.

## THE MEANING AND CAUSES OF PROTEIN DEFICIT

Protein is a fundamental building material of living cells. It is required for growth and maintenance of all tissues. Whenever these processes are retarded or impaired, a deficit of protein may be presumed to exist, even though the plasma protein concentration may not be diminished. In this sense, osteoporosis (or deficiency of matrix formation) is evidence of protein deficit, as is emaciation of muscle and skin, or retardation of growth in general.[13]

A deficit of protein may result from many causes, some of which are outlined in Table I. In many disease conditions more than one factor may be involved and their relative importance difficult to determine.

## THE DYNAMIC EQUILIBRIUM OF BODY PROTEINS

From the classic investigations of the late Schoenheimer[14] has emerged the concept of metabolic regeneration of tissues by means of continual release and uptake of metabolic substrates to and from a circulating metabolic pool, through which all constituents of the body are in dynamic equilibrium. This has since been established as one of the most significant facts in modern biochemistry.

In experiments with dogs made anemic or hypoproteinemic by repeated bleeding or plasmaphoresis, Whipple[15] found that muscle, liver, and other tissue proteins were regularly mobilized to replenish the hemoglobin and plasma proteins depleted under his experimental conditions. This he termed "raiding of the body protein stores." In other experiments he also demonstrated the transformation of parenterally administered $C^{14}$-labeled plasma proteins to organ proteins. From these observations he concluded that within the total mass of body proteins there was a steady interchange between proteins in circulation, in extracellular fluids, in the cells, and in the reserve stores.

## RAIDING OF BODY PROTEIN STORES—A COMPENSATORY MECHANISM

The propriety of the term "body protein stores" has been questioned on the ground that there is no known organ having the primary function of a mobile reserve of protein.[8, 16, 17] Physiologically, nonetheless, all body proteins are in dynamic equilibrium and are more or less mobilizable.[14, 15] In this sense the usage of the term seems justified.

From Whipple's experiments and other observations (vide infra), it would appear that "to rob Peter to pay Paul" is a deliberate way the body manages its protein economy under adverse conditions. This is by no means unique to protein metabolism; indeed, it seems a common physiologic phenomenon (witness the maintenance of acid-base balance, of blood sugar level, electrolyte equilibrium and calcium homeostasis through similar compensatory mechanisms).

In such operations, it seems as if the body has a priority system to regulate the alloca-

tion and transfer of metabolic substances among its many organs in accord with their current needs and their physiologic importance to the total well-being of the organism. For instance, in pregnancy the development of the fetus has the highest priority; if fetal needs are not adequately met by dietary intake, maternal resources are relentlessly utilized, and the mother may develop anemia, weight loss, osteoporosis, and other evidences of deficiency. During the migration of the salmon from the sea to its spawning grounds, the fish is known not to consume any food. In addition to its prodigious effort, it also has to provide protein and other nutrient materials for the tremendous growth of the generative organs during the journey. These needs, unprovided for during starvation, are apparently fulfilled by increased catabolism of muscle substance, which has been known for some time,[18] and by the development of osteoporosis, which has recently been identified.[19]

We are inclined to believe that our patients with liver diseases might have developed more serious hypoproteinemia and anemia, if the bones had not become osteoporotic or the muscle and skin had continued to grow normally.

It seems of some importance to clarify the proper meaning of the word "robbing" or "raiding" of protein stores in the above discussion with respect to the pathogenesis of osteoporosis. The phrase appears to carry the connotation of increased removal of organ protein. This may be true with muscle or liver.[15] In the case of bone, however, the implication of increased resorption is contrary to the accepted pathophysiologic concept of osteoporosis; although more recently the possibility of increased resorption of bone without increased osteoclastic activity has been suggested.[2] In any event, there need be no contradiction, if by *robbing* or *raiding* is meant *depriving* or *diverting* of protein supplies en route to bone. In a dynamic economy such deprivation or diversion may lead to diminished matrix production; and while physiologic resorption continues, a net decrease of bone mass—osteoporosis will occur. In the period of rapid growth this may develop more readily and more severely.

**Table II.** Body protein stores*

| *Body organs* | *Organ weight as % of body weight* | *Organ protein as % of organ weight* | *Organ protein as % of body weight* | *Organ protein as % of body protein* |
|---|---|---|---|---|
| Whole body | 100 | 15 to 20 | 15 to 20 | 100 |
| Muscle | 30 to 40 | 20 | 6 to 8 | 40 |
| Bone | 10 to 18 | 22 to 28 | 2 to 5 | 14-25 |
| Skin | 8 | 25 to 30 | 2 to 2.5 | 10-12 |
| Red blood cell (Hg) | 4 | 33 | 1.3 | 6 to 8 |
| Liver | 3 | 20 | 0.6 | 3 to 4 |
| Plasma | 5 | 6 to 8 | 0.3 to 0.4 | 2 |

*Values given in first and second columns are from published data in the literature,[21-24] those given in third and fourth columns are derived from the first 2 columns. They provide a quantitative basis for the hypothesis that osteoporosis is a compensatory mechanism in a situation of protein deficit.

## THE EFFECTS OF HORMONES ON PROTEIN METABOLISM AND OSTEOPOROSIS

Generally speaking, hormones function as metabolic regulators. They act by accelerating or inhibiting the rate of cellular enzymatic reactions and thus exert regulatory influence in physiologic processes concerned with the maintenance of homeostasis. In the case of protein metabolism, it has been postulated that an excess of adrenal oxycorticosteroids may decrease the rate of synthesis or increase the rate of breakdown, that an excess of thyroxin may increase catabolism, and that a deficiency of the sex hormones or adrenal androgens may decrease anabolism.[6, 11, 20] More recently, the emphasis has been on a relative imbalance between the anabolic effects of the sex and adrenal androgens on one hand and the antianabolic activities of the adrenal oxycorticosteroids on the other.[6] In liver diseases, or, indeed, in any disease associated with secondary hormonal disturbance, such relative imbalance may in part account for the occurrence of a protein deficit.

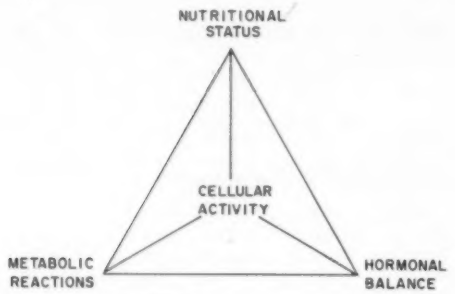



**Fig. 1.** The tetrahedral of interdependence between nutritional status, hormonal balance, metabolic reactions, and cellular activity. Each factor influences and is in turn influenced by the other factors.

Although these postulates have received considerable support from experimental and clinical observations, the precise mechanism of hormone action at the enzymatic and substrate levels, however, remains to be elucidated.[9]

Pritchard[7] has propounded that the osteoblasts, the osteoclasts, and the marrow reticulum cells are mutually convertible; that in their transformations lies the heart of every problem of bone physiology and pathology; and that in response to physiologic or pathologic stimuli, these cells may differentiate in the direction of osteoblastic or osteoclastic activity.[7]

Since hormonal balance, nutritional status, and metabolic reactions are interdependent, and disturbance of any one factor invariably causes disturbance of the other two, the question of which one is the most important seems moot. It appears logical that either one of the 3—hormonal imbalance, metabolic disorders, or nutritional deficiency—may directly or indirectly influence cellular transformation in the direction of diminished osteoblastic differentiation with consequent osteoporosis (Fig. 1).

## QUANTITATIVE CONSIDERATIONS AND THE INFLUENCE OF AGE

The muscle, the bone, and the skin, because of their bulk, contain the largest shares of the total mass of body proteins. By comparison, the liver and the circulating plasma contain relatively insignificant amounts of protein. This is shown in Table II.[21-24]

The quantitative aspects of protein loss in osteoporosis are of considerable interest but have not received enough attention.[1, 25] Although a generalized process, the extent of osteoporosis may vary in different bones and indeed, in different portions of the same bone in the early stages. Such variations, however, tend to disappear as osteoporosis progresses. Careful studies[12] have shown that 30 to 50 per cent of osseous substance must be lost before osteoporosis becomes demonstrable with certainty by roentgenography. The quantity of osseous protein involved is considerable.

Let us consider the 2½-year-old girl with primary hepatoma[10] who was markedly osteoporotic and weighed only 10 kilograms, instead of 15 kilograms for the 50th percentile for her age. Assuming that she lost 50 per cent of the osseous substance, it is estimated that she lost 165 Gm. of protein from the bones. This amount is equivalent to 7 per cent of the total body protein, 2 times the total liver protein, and 3 times the total plasma protein. Yet, she made a rapid recovery after the tumor was removed surgically. These data are shown in Table III.

Let us also consider a hypothetical woman patient who is 60 years old, stands 5 feet tall, weighs 60 kilograms, and has moderately severe postmenopausal osteoporosis. Again assuming a 50 per cent loss of osseous substance, the protein loss from the bones is estimated to be about 1,000 Gm. This represents 8 to 10 per cent of the total body protein, 3 times the total liver protein, and 5 times the total plasma protein. She shows little response to hormonal and dietary therapy over a long period of time. These data are also shown in Table III.

These quantitative data, crude as they are, illustrate the order of magnitude of protein deficit in osteoporosis. In the case of the child with hepatoma this was comparatively small and apparently readily restored after the cause was removed. Undoubtedly, the great capacity to achieve sustained posi-

tive nitrogen balance and the great potential for growth and repair characteristic of childhood are important factors in favor of rapid recovery. On the other hand, in the patient with postmenopausal osteoporosis, the protein deficit of 1,000 Gm. is 6 times greater than that of the child. In addition, at her age, the ability to maintain positive nitrogen balance, even with the best of diet, and the potential for growth and repair, even with optimal substitutional hormonal therapy, are greatly diminished. It is not surprising that the osteoporosis does not show notable improvement. Indeed, mere prevention of further progress and maintenance of status quo are regarded as successful treatment.[5, 6, 11]

Between these extreme examples, there is a wide range of variability and a large number of variables such as age, nutrition, endocrine balance, liver, and gastrointestinal function, as well as the severity of the osteoporosis and the reversibility of the underlying disease or diseases. It is obvious that the prognosis of osteoporosis must be individualized and based upon due considerations of all pertinent factors.

In addition to the points already alluded to with respect to the influence of age upon the healing of osteoporosis, the following comments may be added: In infancy and early childhood osteoporosis appears more readily. This is probably related to the large requirement of protein to maintain the high rate of growth and to the small bulk of bone which is scarcely mature and apparently more labile, a situation not unlike the instability of fluid balance and the propensity to dehydration in the same period of life. As the child grows older and the bones grow bigger and stronger, he attains a larger and more stable osseous mass, and it takes a longer period of time for osteoporosis to become apparent. After adulthood is reached and the skeleton has fully matured, the development of osteoporosis becomes even more insidious, because with cessation of growth, the requirement of protein is decreased; also, the bulk of bone involved is much larger.

**Table III.** Protein deficit in osteoporosis*

| | *2½-year-old girl* | | *60-year-old woman* | |
|---|---|---|---|---|
| | *Normal (kg.)* | *Hepatoma with osteoporosis (kg.)* | *Normal (kg.)* | *Postmenopausal osteoporosis (kg.)* |
| Body weight | 15 | 10 | 60 | 50 |
| Body protein | 3 | 2 | 12 | 10 |
| Bones | 1.5 | 0.75 | 8 | 4 |
| Bone protein | 0.165 | 0.165 | 2 | 1 |
| Protein deficit | | 0.165 | | 1 |

*Values given are derived from data presented in Table II.

From the data in Table II it may be noted that the liver accounts for 3 to 4 per cent and the plasma about 2 per cent of the total body protein. In contrast, the skeletal muscle, the bone, the skin, and the red cells (hemoglobin) account for much larger shares. The liver is the principal site of plasma protein synthesis[26, 27] and the plasma proteins have been regarded as transport proteins.[15, 27] When dietary intake and intestinal and hepatic functions are normal, the amino acids and plasma proteins in circulation, constantly replenished by the liver, are sufficient to meet the normal demand of the body tissues. However, when a deficit of protein develops from deficient intake, increased destruction, abnormal loss, or increased requirement (Table I), the meager resources of liver and plasma proteins may become insufficient to cope with the demand. When this happens, rationing of available resources in accordance with a priority system may become imperative. Invariably, so it seems, the organs with large protein reserves may be deprived of their normal quota of protein supply, which is diverted to fill more urgent needs elsewhere. Meanwhile, however, the normal wear and tear in the deprived organs continue without being repaired. Eventually atrophic changes and growth retardation ensue. It is through such compensatory mechanisms that the

plasma protein and hemoglobin concentrations may be maintained at nearly normal levels. To accomplish this, however, the structural and functional integrity of the liver are important factors. With serious decompensation of hepatic function, such as in severe liver cirrhosis, hypoproteinemia and anemia eventually occur.

## SUMMARY AND CONCLUSIONS

1. Our observations of children with hepatic glycogenosis, hepatic tumors, and hepatic cirrhosis, as reported separately in this issue, lead us to believe that the high incidence of osteoporosis, often accompanied by atrophy of muscle and skin and retardation of growth and development, may represent a nonspecific manifestation of a systemic deficit of protein.

2. This protein deficit, often relative and inapparent, may be the result of many causes directly or indirectly attributable to the liver disease involved, with or without manifest hepatic insufficiency. These have been discussed in the preceding paper.

3. We propose that the occurrence of osteoporosis and other atrophic changes represents a compensatory mechanism by which the body regulates its protein economy under stringent circumstances of diminished supply, abnormal demand, and/or increased destruction, in much the same manner as in other well-known physiologic phenomena of homeostasis.

4. A system of priority for the allocation and transfer of available proteins seems operative. A body organ receives, or is deprived of, a rationed amount of protein in accordance with its current needs appropriate to its priority rating. This is possible because all body constituents are in a state of flux, all body proteins are in equilibrium, and all living tissues degenerate and regenerate continually.

5. In such compensatory operations, the organs with large shares of body proteins and low priority ratings, such as the muscle, the bone, and the skin, may be deprived of their normal supply or depleted of their reserve store of proteins. In either case, their growth may be impaired and atrophic changes may ensue. Advantage is taken of the diverted supply and mobilized reserve to fill the needs of repair of organs with greater physiologic importance.

6. The important role of the hormones in the regulation of protein metabolism and cellular activity with respect to the pathogenesis of osteoporosis has been discussed.

7. The quantitative aspects of osteoporosis and the influence of age upon the rapidity of development and of repair of osteoporosis have been considered.

We wish to thank Dr. A. Baird Hastings and Dr. Franklin C. McLean for their encouragement and suggestions.

## REFERENCES

1. Albright, F., and Reifenstein, E. S.: Parathyroid Glands and Metabolic Bone Disease, Baltimore, 1948, Williams & Wilkins Company, pp. 145-204.
2. Sissons, H. A., Osteoporosis in Cushing's Syndrome, in Rodahl, K., Nicholson, J. R., and Brown, E. M., editors: Bone as a Tissue, New York, 1960, McGraw-Hill Book Company, pp. 3-17.
3. Urist, M. R.: Observations Bearing on the Problems of Osteoporosis, in Rodahl, K., Nicholson, J. R., and Brown, E. M., editors: Bone as a Tissue, New York, 1960, McGraw-Hill Book Company, pp. 18-45.
4. Nordin, B. E.: Osteoporosis and Calcium Deficiency, in Rodahl, K., Nicholson, J. R., and Brown, E. M., editors: Bone as a Tissue, New York, 1960, McGraw-Hill Book Company, pp. 46-66.
5. Whedon, G. D.: Osteoporosis: Atrophy of Disuse, in Rodahl, K., Nicholson, J. R., and Brown, E. M., editors: Bone as a Tissue, New York, 1960, McGraw-Hill Book Company, pp. 67-82.
6. Reifenstein, E. S.: Osteoporosis: Discussion, in Rodahl, K., Nicholson, J. R., and Brown, E. M., editors: McGraw-Hill Book Company, New York, 1960, pp. 83-99.
7. Pritchard, J. J.: The Osteoblasts, in Bourne, G. H., editor: The Biochemistry and Physiology of Bone, New York, 1956, Academic Press, Inc., pp. 81-103.
8. Dumm, M. E., and Ralli, E. P.: The Hormonal Control of Metabolism in Wohl, M. G., and Goodhart, R. S., editors: Modern Nutrition in Health and Disease, Philadelphia, 1960, Lea & Febiger, pp. 61-81.
9. White, A.: The Interaction of Enzymes and Hormones, Pediatrics 26: 476, 1960.

10. Teng, C. T., Daeschner, C. W., Jr., Singleton, E. B., and Rosenberg, H. S., Cole, V. W., Hill, L. L., and Brennan, J. C.: Liver Diseases and Osteoporosis in Children. I. Clinical Observation, J. PEDIAT. 59: 684, 1961.
11. Albright, F.: Osteoporosis, Ann. Int. Med. 27: 861, 1947.
12. Babaiantz, P. L.: Les osteoporoses, Radiol. Clin. 16: 291, 1947.
13. Follis, R. H., Jr.: Deficiency Disease, Springfield, Ill., 1958, Charles C Thomas, Publisher, pp. 333-349.
14. Schoenheimer, R.: The Dynamic State of Body Constituents, Cambridge, 1946, Harvard University Press.
15. Whipple, G. H.: The Dynamic Equilibrium of Body Proteins, Springfield, Ill., 1956, Charles C Thomas, Publisher.
16. Lowe, C. U.: The Relation Between Cell Structure and Cell Function, Pediatrics 26: 454, 1960.
17. Geiger, E.: Digestion, Absorption and Metabolism of Protein, in Wohl, M. G., and Goodhart, R. S., editors: Modern Nutrition in Health and Disease, Philadelphia, 1960, Lea & Febiger, pp. 136-140.
18. Meischer: Die Histochemischen and Physiologischen Arberten, Vogel, Leipzig, 1897 (quoted by Geiger).
19. Thomas, S. F.: Personal communication, 1960.
20. Albright, F.: The Effect of Hormones on Osteogenesis in Man, in Pincus, G., editor: Recent Progress in Hormone Research, New York, 1947, Academic Press, Inc., vol. 1, pp. 293-353.
21. Follis, R. H., Jr.: Deficiency Disease, Springfield, Ill., 1957, Charles C Thomas, Publisher, p. 6.
22. West, E. S., and Todd, W. R.: Textbook of Biochemistry, New York, 1951, The Macmillan Company, pp. 406-410.
23. Mitchell, H. H., Hamilton, T. S., Steggerda, F. R., and Bean, H. W.: The Composition of the Adult Human Body and Its Bearing on the Biochemistry of Growth, J. Biol. Chem. 158: 625, 1945.
24. Dickerson, J. W. T.: Personal communication, 1960.
25. Moldawer, M.: Osteoporosis (unpublished review), 1960.
26. Miller, L. L., Bly, C. G., Watson, M. L., and Bale, W. F.: The Dominant Role of the Liver in Plasma Protein Synthesis, J. Exper. Med. 94: 431, 1951.
27. Anker, H. S.: The Biosynthesis of Plasma Proteins, in Putnam, F. W., editor: The Plasma Proteins, New York, 1960, Academic Press, Inc., vol. 2, pp. 267-307.

# *Relation of lung volumes to height in healthy persons between the ages of 5 and 38 years*

**Charles D. Cook, M.D.,* and Joanna F. Hamann, B.A.**

BOSTON, MASS.

THE application of laboratory techniques to the study of respiratory abnormalities in infants, children, and adults has led to the need for the establishment of normal values for a variety of lung functions. The measurement of lung volumes, especially total lung capacity, vital capacity, functional residual capacity, and residual volume, has become a standard procedure in the assessment of pulmonary status; this report presents data on the relation between these lung volumes and height in normal persons of both sexes ranging in age from 5 to 38 years.

## SUBJECTS AND METHODS

Approximately three quarters of the 171 individuals, of whom 85 children have previously been reported,[1] were healthy volunteers without histories of chronic respiratory or cardiac disease. Approximately one quarter were children hospitalized for elective surgical procedures who were studied either before or more than 3 days after operation. Persons familiar with the procedures or trained subjects comprised less than 6 per cent of the total. The 106 males (age range, 5 to 38 years) varied in height from 110 to 203 cm. and the 65 females (5 to 25 years) varied from 105 to 183 cm.

The measurement of the lung volumes was made by spirometry and the closed-circuit helium dilution technique.[1, 2] All measurements were done in the same laboratory and all were done in duplicate. The basic measurement of functional residual capacity had a standard error of ± 75 ml. when done in duplicate and the average of the 2 values was used; the larger of the expiratory and inspiratory reserve values was used for the calculation of residual volume, vital capacity, and total lung capacity. The results were expressed in liters BTPS and related to the subject's height in centimeters; in one instance (VC for males) the relation between a lung volume and surface area estimated from the nomogram of Consolazio, Johnson and Marek[3] was calculated.

## RESULTS

The results of the studies are shown in the form of regression equations in Table I

*From the Department of Medicine, Children's Hospital Medical Center, and the Department of Pediatrics, Harvard Medical School, Boston.*

*Supported by Grant H-5339 from the National Institutes of Health, Public Health Service.*

**Address, The Children's Medical Center, 300 Longwood Avenue, Boston 15, Mass.*

and the individual data are plotted against height in Figs. 1 to 4. Figs. 5 and 6 show the similarity of the slopes of the regression lines for residual volume, functional residual capacity, vital capacity, and total lung capacity related to height in both males and females. One standard error of the estimate around the arithmetic mean is shown so that these charts may be used for comparison with values obtained in patients of various sizes. In Fig. 7 are shown the present data for vital capacity combined with that obtained in newborn infants by Sutherland and Ratcliff.[9]

## DISCUSSION

As recently pointed out by Hepper, Fowler, and Helmholz,[4] Kelly,[5] in a study of vital capacity of boys and girls, first identified the relation between a lung volume and the cube of height. Bateman,[6] Morse, Schultz, and Cassels,[7] Engström and co-workers[8] and Helliesen and associates[1] have also variously described this relation in adults and children. Hepper and co-workers[4] themselves confirmed such a relationship for the vital capacity and total lung capacity of tall men. Since volume is three dimensional it might be expected that lung volumes would be related to the cube of a one dimensional measurement such as height. The fact that this relation applies with an excellent correlation to individuals of both sexes and with a wide range of heights indicates that height is a reliable basis for the prediction of these lung volumes. Although in persons of normal body proportions there might be a good correlation with body weight and/or surface area (a good correlation [r = .94] between body surface area and the vital capacity of the males was found in the present series [Table I]), it would be expected that the correlation with either weight or surface area would be less reliable with either thin or overweight individuals.

In a recent report, Sutherland and Ratcliff[9] have reported "crying vital capacity" measurements in 93 normal infants under 4 days of age. With the combination of their data for the 53 full-term infants whose length was measured and the data of the present report, regression lines for males and females have been calculated (Table I), and again a close relation between vital capacity and the cube of height was found (Fig. 7).

The finding that there was no significant difference between the regression lines for residual volume and functional residual capacity for males and females was consistent with the results reported by Engström and co-workers[8] who found no significant differences for all 4 lung volumes in their 50 boys and 43 girls. However, in the present series, males were found to have slightly,

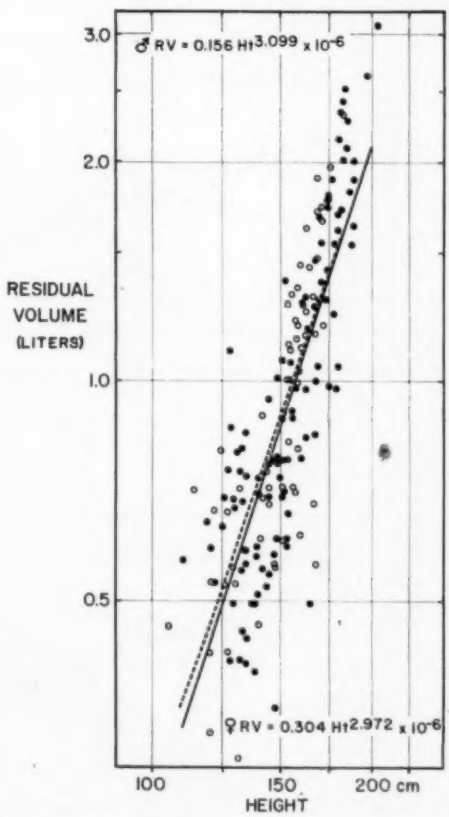



**Fig. 1.** Measurements of residual volume plotted against height for 106 males (●) and 65 females (o). There was no significant difference between the regression line for males (solid line) and that for females (dotted line). The equations and lines are for geometric means.

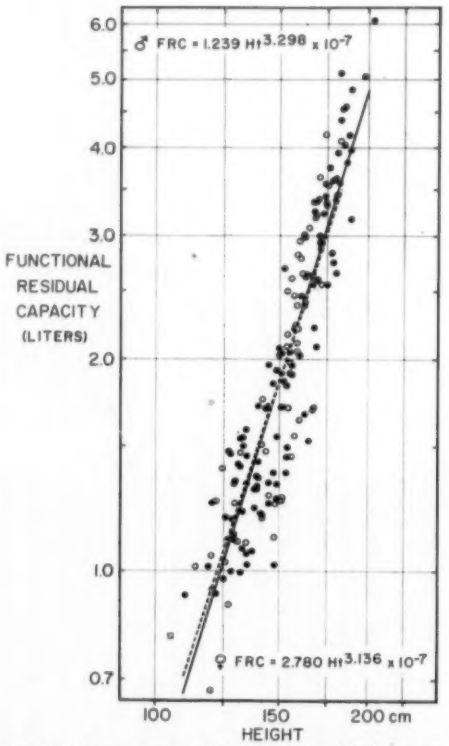



Fig. 2. Measurements of functional residual capacity plotted against height for 106 males (●) and 65 females (o). There was no significant difference between the regression line for males (solid line) and that for females (dotted line). The equations and lines are for geometric means.

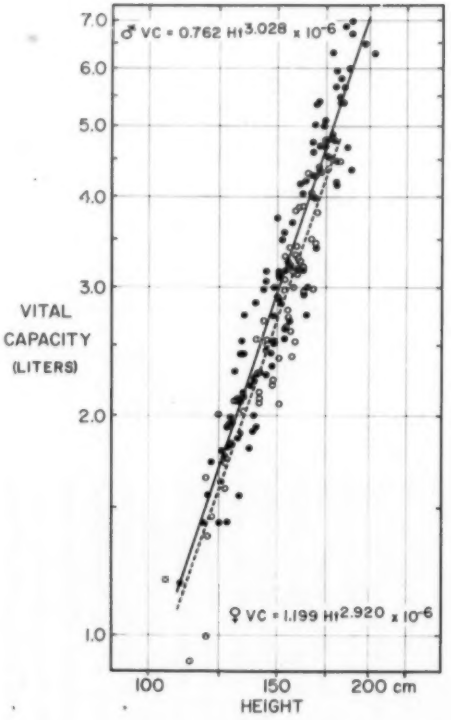



Fig. 3. Measurements of vital capacity for 106 males (●) and 65 females (o). There was a significant ($p = <.01$) difference between the regression line for males (solid line) and that for females (dotted line). The equations and lines are for geometric means.

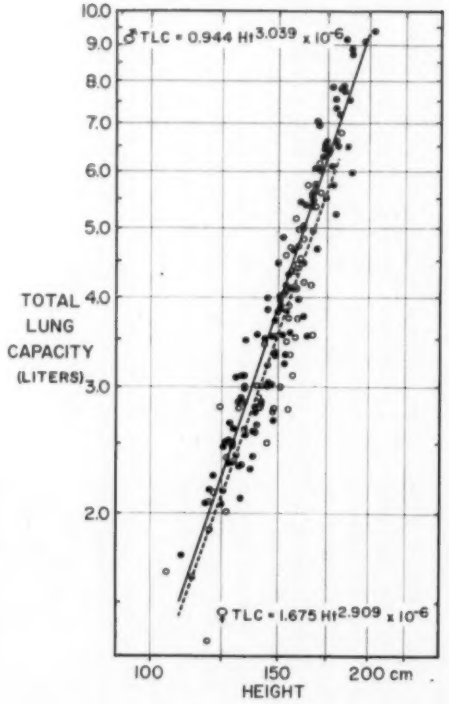



Fig. 4. Measurements of total lung capacity for 106 males (●) and 65 females (o). There was a significant ($p = <.01$) difference between the regression line for males (solid line) and that for females (dotted line). The equations and lines are for geometric means.

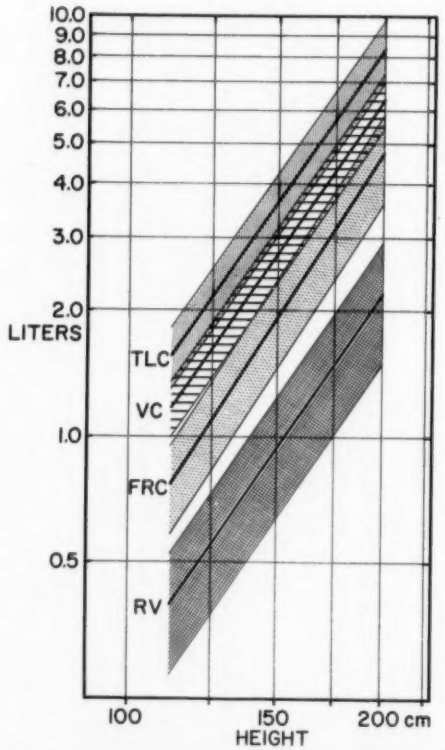



Fig. 5. Regression lines for lung volumes versus height in 106 males (1 S.D. around the arithmetic mean is shown).

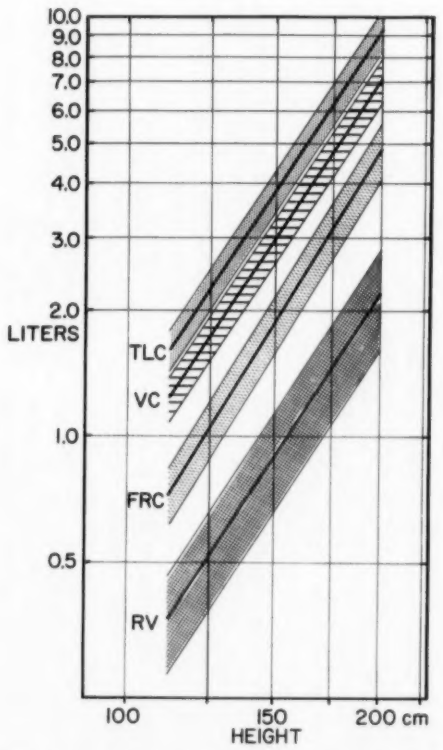



Fig. 6. Regression lines for lung volumes versus height in 65 females (1 S.D. around the arithmetic mean is shown).

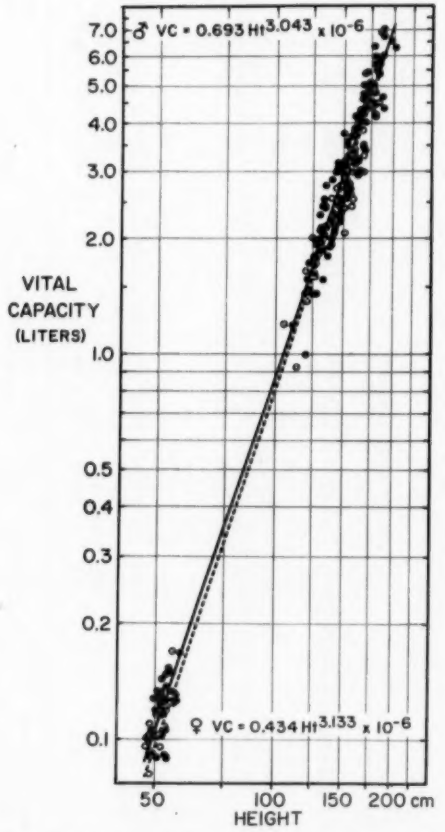



Fig. 7. Vital capacity versus height for males and females (●) with the data of Sutherland and Ratcliff[9] for newborn infants included.

**Table I.** Relation between lung volumes and body size

| *Lung volume* | *No. of subjects* | *Regression equation** | *S. E. of Mean†* (%) | *Correlation coefficient* |
|---|---|---|---|---|
| *Males‡* | | | | |
| RV | 106 | $RV = .162 \times Ht.^{3.099} \times 10^{-6}$ | ± 27 | .79 |
| FRC | 106 | $FRC = 1.254 \times Ht.^{3.298\ 5} \times 10^{-7}$ | ± 16 | .92 |
| VC | 106 | $VC = .767 \times Ht.^{3.028} \times 10^{-6}$ | ± 12 | .95 |
| VC | 105 | $VC = 3.555 \times BSA - 1.67$ | ± 14 | .94 |
| VC§ | 137 | $VC = .707 \times Ht.^{3.043} \times 10^{-6}$ | ± 15 | .995 |
| TLC | 106 | $TLC = .950 \times Ht.^{3.039} \times 10^{-6}$ | ± 11 | .96 |
| *Females‖* | | | | |
| RV | 65 | $RV = .320 \times Ht.^{2.972} \times 10^{-6}$ | ± 32 | .77 |
| FRC | 65 | $FRC = 2.861 \times Ht.^{3.136} \times 10^{-7}$ | ± 24 | .86 |
| VC | 65 | $VC = 1.213 \times Ht.^{2.920} \times 10^{-6}$ | ± 15 | .94 |
| VC§ | 87 | $VC = .437 \times Ht.^{3.133} \times 10^{-6}$ | ± 12 | .996 |
| TLC | 65 | $TLC = 1.698 \times Ht.^{2.909} \times 10^{-6}$ | ± 17 | .92 |

*Volumes in liters BTPS; height in centimeters; body surface area (BSA) in square meters; regression equations are for arithmetic mean rather than geometric means shown in Figs. 1 to 4. Arithmetic means are used for greater ease in calculating predicted values and the standard error of the estimate. RV = residual volume; FRC = functional residual capacity; VC = viral capacity; TLC = total lung capacity.

†Expressed as per cent of arithmetic mean.

‡Age range 5 to 38 years, mean height = 153 cm. (range 110 to 203).

§Includes data of Sutherland and Ratcliff[9] for newborn infants.

‖Age range 5 to 25 years; mean height = 149 cm. (range 105 to 183).

but significantly, larger vital capacities and total lung capacities.

## SUMMARY

The results of the measurement of residual volume, functional residual capacity, vital capacity, and total lung capacity in 171 persons between the ages of 5 and 38 years have been reported together with regression equations based on height. The lung volumes correlated well with the cube of height. A similar relationship was found when the values of Sutherland and Ratcliff for "crying vital capacity" of newborn infants were combined with the present measurements of vital capacity in children and young adults.

## REFERENCES

1. Helliesen, P. J., Cook, C. D., Friedlander, L., and Agathon, S.: Studies of Respiratory Physiology in Children I. Mechanics of Respiration and Lung Volumes in 85 Normal Children 5 to 17 Years of Age, Pediatrics **22:** 80, 1958.
2. Gilson, J. C., and Hugh-Jones, P.: Lung Functions in Coalworkers' Pneumoconiosis, Medical Research Council Special Reports Series, No. 290, London, 1955, Her Majesty's Stationery Office.
3. Consolazio, C. F., Johnson, R. E., and Marek, E.: Metabolic Methods, St. Louis, 1951, The C. V. Mosby Company, p. 338.
4. Hepper, H. G. G., Fowler, W. S., and Helmholz, H. F., Jr.: Relationship of Height to Lung Volume in Healthy Men, Dis. of Chest **37:** 1960.
5. Kelly, H. G.: A Study of Individual Differences in Breathing Capacity in Relation to Some Physical Characteristics, University of Iowa Studies, Studies in Child Welfare VII, 1933.
6. Bateman, J. B.: Studies of Lung Capacities and Intrapulmonary Mixing: Normal Lung Capacities, J. Appl. Physiol. **3:** 133, 1950.
7. Morse, M., Schultz, F. W., and Cassels, D. E.: The Lung Volume and Its Subdivisions in Normal Boys 10-17 Years of Age, J. Clin. Invest. **13:** 380, 1952.
8. Engström, I., Karlberg, P., and Kraepelien, S.: Respiratory Studies in Children I. Lung Volumes in Healthy Children 6-14 Years of Age, Acta paediat. **45:** 277, 1956.
9. Sutherland, J. M., and Ratcliff, J. W.: Crying Vital Capacity, A. M. A. J. Dis. Child. **101:** 67, 1961.

# *Birth weight of infants with cyanotic and acyanotic congenital malformations of the heart*

**Ali Mehrizi, M.D., and Allan Drash, M.D.**

BALTIMORE, MD.

OBSERVATIONS in the Harriet Lane Home Cardiac Clinic led us to believe that the birth weight of infants with complete transposition of the great vessels tended to be higher than the average birth rate of normal infants. A survey of the literature revealed no study of the birth weight of infants with congenital malformations of the heart. Since it has been shown that the average birth weight of white infants is higher than that of Negro newborn infants, and since our clinic population is composed mainly of white children, this study was restricted to the birth weight of white infants.

## MATERIAL

This study was divided into 4 groups: (1) children with cyanotic congenital heart defects, (2) children with acyanotic congenital heart defects, (3) a control group of infants referred for evaluation of a functional murmur, and (4) a second control group of white infants born in the City of Baltimore during 1956.

Group I comprised 341 white infants with cyanotic congenital heart defects. Our first analysis of these infants revealed that the birth weight of infants with transposition of the great vessels was significantly higher than the birth weight of infants with other cyanotic congenital malformations. We therefore divided Group I into 2 categories, (a) a group of 117 cases with transposition of the great vessels, and (b) a group of 224 cases with other cyanotic congenital malformations, composed of 136 cases of tetralogy of Fallot, 37 cases of truncus arteriosus, 40 cases of tricuspid atresia, and 11 cases of defective development of the right ventricle with severe pulmonary stenosis or atresia. The birth weights of the infants in the second group (i.e., that of 224 cases) have not been classified into categories, as it was found that the birth weights of infants with these various malformations was practically the same. In those infants with transposition of the great vessels, the average birth weight was 7.6 pounds and in all other cyanotic malformations the average birth weight was 6.96 pounds.

Group II consisted of 259 infants with acyanotic congenital heart defects, as follows: 89 cases of patent ductus arteriosus, 42 cases of ventricular septal defects, 71 cases of atrial septal defects, 18 cases of coarctation of the aorta (preductal and post-

*From the Cardiac Clinic of the Harriet Lane Home and the Department of Pediatrics, The Johns Hopkins University School of Medicine.*

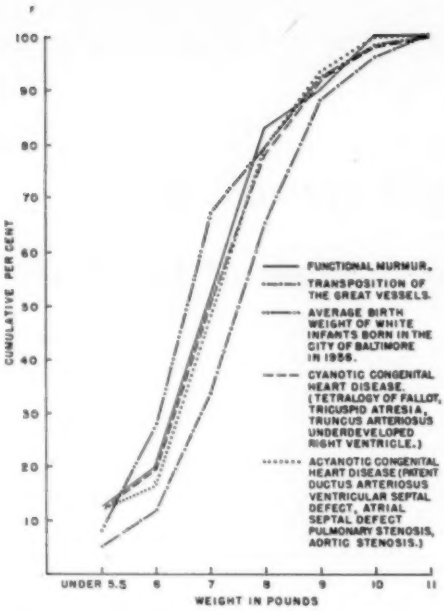



**Fig. 1.** Cumulative indices.

ductal), 19 cases of aortic stenosis, 20 cases of pulmonary valvular stenosis. Analysis of this group showed that the birth weight, regardless of the specific malformation, was virtually the same with only insignificant differences. In this group the average birth weight was 6.97 pounds.

Group III consisted of 70 patients diagnosed as having a functional murmur. These patients were otherwise normal, entirely asymptomatic children in whom heart murmurs had been heard on routine physical examination, and who were then referred to the Harriet Lane Home Cardiac Clinic for evaluation. We chose their birth weight as a control, because they were referred to us in the same manner as were those with definite malformations and, to the best of our knowledge, came from homes of similar economic status. In this group, the average birth weight was closely similar to the second group, namely, 6.92 pounds.

Group IV comprised 14,007 white infants born in the City of Baltimore during 1956.[1] We used these as a second control because this was a large and unselected group. The average birth weight of the group was 6.96 pounds.

## RESULTS

Analyses of the birth weights of the above groups showed that the average birth weight of infants with complete transposition of the great vessels was 7.60 pounds whereas the average birth weight of infants with other cyanotic malformations was 6.96 pounds and of those with acyanotic malformations was 6.97 pounds. In the 2 control groups, that is, those with functional murmurs and the white infants born in the City of Baltimore, the average birth weights were 6.92 and 6.96 pounds, respectively. Thus the infants with transposition of the great vessels were on the average heavier at birth than any of the other groups. It is important to empha-

**Table I.** Complete transposition of the great vessels (distribution of 117 cases according to birth weight)

| *Birth weight (lb.)* | *No. of cases* | *% of total No.* | *Cumulative No. of cases* | *Cumulative %* |
|---|---|---|---|---|
| 5.5 or under | 6 | 5.12 | 6 | 5.0 |
| 5.6 to 6.0 | 8 | 6.83 | 14 | 12.0 |
| 6.1 to 7.0 | 26 | 22.22 | 40 | 34.0 |
| 7.1 to 8.0 | 37 | 31.62 | 77 | 65.0 |
| 8.1 to 9.0 | 27 | 23.07 | 104 | 88.0 |
| 9.1 to 10.0 | 8 | 6.83 | 112 | 95.7 |
| 10.1 to 11.0 and over | 5 | 4.27 | 117 | 100.0 |

**Table II.** Other cyanotic malformations of the heart (distribution of 224 cases according to birth weight)

| *Birth weight (lb.)* | *No. of cases* | *% of total No.* | *Cumulative No. of cases* | *Cumulative %* |
|---|---|---|---|---|
| 5.5 or under | 28 | 12.50 | 28 | 12.5 |
| 5.6 to 6.0 | 17 | 7.58 | 45 | 20.1 |
| 6.1 to 7.0 | 69 | 30.80 | 114 | 51.0 |
| 7.1 to 8.0 | 60 | 26.78 | 174 | 78.0 |
| 8.1 to 9.0 | 32 | 14.28 | 206 | 92.0 |
| 9.1 to 10.0 | 13 | 5.80 | 219 | 98.0 |
| 10.1 to 11.0 | 3 | 1.33 | 222 | 99.0 |
| 11.0 to 12.0 | 2 | 0.88 | 224 | 100.0 |

**Table III.** Acyanotic malformations of the heart (distribution of 259 cases according to birth weight)

| *Birth weight (lb.)* | *No. of cases* | *% of total No.* | *Cumulative No. of cases* | *Cumulative %* |
|---|---|---|---|---|
| 5.5 or under | 32 | 12.35 | 32 | 12.4 |
| 5.6 to 6.0 | 11 | 4.24 | 43 | 16.6 |
| 6.1 to 7.0 | 79 | 30.50 | 122 | 47.2 |
| 7.1 to 8.0 | 81 | 31.27 | 203 | 78.0 |
| 8.1 to 9.0 | 38 | 14.67 | 241 | 93.0 |
| 9.1 to 10.0 | 16 | 6.17 | 257 | 99.0 |
| 10.0 to 11.0 | 2 | 0.77 | 259 | 100.0 |

size that none of the infants with complete transposition of the great vessels showed signs or symptoms of cardiac failure and none were edematous at the time of delivery.

Because these averages might be readily altered by a few extremely heavy or exceptionally light infants, each group was analyzed to determine the number of infants of various birth weights. The birth weights were divided in units of pounds except that all premature infants, that is, those with a birth weight of 5.5 pounds or under, were grouped together and the next unit was composed of infants between 5.6 and 6 pounds inclusive. The results are given in Tables I to V. From these tables, the cumulative indices and the distribution curves were plotted, as shown in Figs. 1 and 2. Both curves show that infants with complete transposition of the great vessels were on the average heavier and those born in Baltimore City appear to be lighter than the 3 other groups.*

## DISCUSSION

The peak of the distribution curves for the 2 control groups and the groups of the other cyanotic malformations occurred in the babies weighing between 6.1 to 7 pounds, whereas in the group of infants with the complete transposition and with the acyanotic malformations the peak occurred at the 7.1 to 8 pound point. Even though the peak was the same in these 2 groups, only 20.8 per cent of all infants in the acyanotic group weighed more than 8 pounds, whereas 34.1 per cent of the infants with complete transposition of the great vessels weighed more than 8 pounds at birth. In the group with other cyanotic malformations, 22.2 per cent of the infants weighed over 8 pounds at birth, whereas in the 2 control groups the percentage of babies weighing more than 8 pounds were 17 per cent and 8 per cent, respectively.

Inasmuch as it is well known that male infants tend to be heavier than female infants, the sex incidence in the various groups was analyzed to ascertain whether this fact in any way affected the birth weight. It was found that the sex ratio in the group of complete transposition of the great vessels was 3 males to 2 females, whereas in the other cyanotic infants and in acyanotic infants the sex ratio was approximately one to one. In the large Baltimore City group the sex ratio was also one to

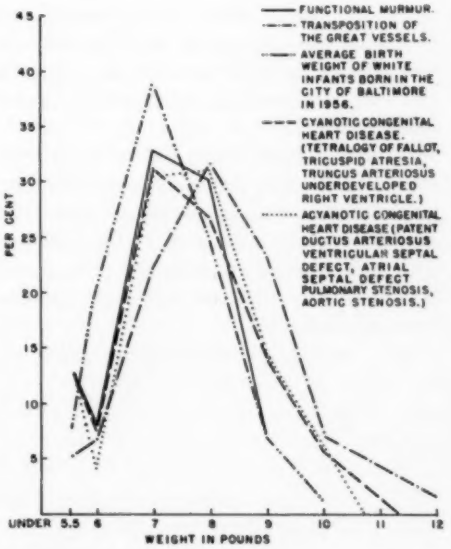



**Fig. 2.** Distribution curves.

*All of the curves except the City of Baltimore curve represent infants who for the most part survived the neonatal period, and consequently these groups have fewer babies of the low birth weight than is found in the City of Baltimore curve.

**Table IV.** Babies who subsequently developed functional murmur (distribution of 70 cases according to birth weight)

| *Birth weight (lb.)* | *No. of cases* | *% of total No.* | *Cumulative No. of cases* | *Cumulative %* |
|---|---|---|---|---|
| 5.5 or under | 9 | 12.8 | 9 | 12.8 |
| 5.6 to 6.0 | 5 | 7.14 | 14 | 20.0 |
| 6.1 to 7.0 | 23 | 32.8 | 37 | 52.8 |
| 7.1 to 8.0 | 21 | 30.00 | 58 | 82.8 |
| 8.1 to 9.0 | 5 | 7.14 | 63 | 90.0 |
| 9.1 to 10.0 | 7 | 9.99 | 70 | 100.0 |

**Table V.** White infants born in the City of Baltimore in 1956 (distribution of 14,007 cases according to birth weight)

| *Birth weight (lb.)* | *No. of cases* | *% of total No.* | *Cumulative No. of cases* | *Cumulative %* |
|---|---|---|---|---|
| 5.5 or under | 1,117 | 7.97 | 1,117 | 8.0 |
| 5.6 to 6.0 | 2,848 | 20.33 | 3,965 | 28.3 |
| 6.1 to 7.0 | 5,453 | 38.93 | 9,418 | 67.2 |
| 7.1 to 8.0 | 3,468 | 24.75 | 12,886 | 92.0 |
| 8.1 to 9.0 | 950 | 6.78 | 13,836 | 98.77 |
| 9.1 to 10.0 | 159 | 1.13 | 13,995 | 99.0 |
| 10.1 to 11.0 | 12 | 0.08 | 14,007 | 100.0 |

one; in the other group, i.e., those with functional murmurs the sex ratio was 3 males to 1 female. Nevertheless, even in this group the percentage of large babies was considerably smaller than in the group of infants with complete transposition of the great vessels.

Further statistical analysis showed that the average birth weight of male to female infants with transposition of the great vessels was 7.8 pounds and 7.2 pounds, respectively, compared with 6.75 pounds and 6.25 pounds in the large control group from the City of Baltimore.

Thus all the evidence indicates that infants with transposition of the great vessels are on the average heavier at birth than other infants and the difference found represents a true difference in birth weights.

The reason that babies with transposition of the great vessels are heavier than other babies is not clear. It is, however, a well-known fact that babies born to prediabetic and diabetic mothers[2] tend to be heavier than those of normal mothers; therefore, it might be significant to study the glucose metabolism of mothers who give birth to infants with transposition of the great vessels. Furthermore, although a detailed study has not been done, we have been impressed by the apparently high incidence of diabetes mellitus in families of patients with transposition of the great vessels.

Finally, it is of importance to note that the incidence of premature babies with transposition of the great vessels was only 5 per cent compared with an incidence of 12.8 per cent of premature infants in Group II and Group III and 8 per cent in babies born in the City of Baltimore. This observation offers further confirmatory evidence that infants with transposition of the great vessels tend to be heavier than the average infant.

We acknowledge with gratitude our debt to Dr. Helen B. Taussig for her help and guidance and we deeply appreciate the constructive criticism of Dr. Janet Hardy and Dr. Catherine Neill in preparing this paper, and we are grateful also for the technical assistance of Mr. T. M. Frazier for evaluation of these figures.

## REFERENCES

1. Annual Report of the Baltimore City Health Department, 1956.
2. Futcher, P. H., and Long, N. W., Jr.: Hospital Data on the Birth of Large Infants to "Pre-diabetic" Women, Bull. Johns Hopkins Hosp. **94**: 128, 1954.

# *Precocious puberty due to secreting chorionepithelioma (teratoma) of the brain*

**Ogden C. Bruton, Colonel, MC, USA,***

**Douglas C. Martz, Captain, MC, USA, and**

**Earl S. Gerard, Major, MC, USA**

EARLY puberty in children with various kinds of brain tumors in the general area of the hypothalamus is not uncommon.[1-3] The hormone release mechanism is not clearly defined in these cases although some investigators have felt that certain of these tumors themselves secrete a hormone which influences sexual development.[4] One case of a primary intracranial chorionepithelioma with metastases to the lungs in a 15-year-old boy is reported in which central nervous system symptoms predominated.[5] Chorionic gonadotropins of high titer were found in the urine, cerebrospinal fluid, and neoplastic tissue, although signs of virilism were not reported. A search of the literature fails to reveal a single instance of a secreting chorionic brain tumor in a male where proof is given that hormonal activity of the tumor was responsible for the changes observed.

We have had the opportunity of observing the development of precocious puberty in a 7-year-old boy which, after prolonged study, was diagnosed as being attributable to a teratoma of the third ventricle which contained a secreting chorionepithelioma. The unique nature of this case and the difficulty in recognizing the cause would seem to justify this report.

*From the Pediatric Service, Pathology Service, and Metabolic Service, Walter Reed General Hospital, Walter Reed Army Medical Center, Washington 12, D. C.*

**Chief, Pediatric Service, Walter Reed General Hospital, Walter Reed Army Medical Center, Washington 12, D. C.*

## CASE REPORT

Four months prior to referral this 7-year-old white boy was noted by his parents to be growing and developing unusually rapidly. The weight increased within this time from 57 pounds to 70 pounds, the shoe size changed from 12½ B to 1 E, and the shirt size from 8 to 10 years. Acne, axillary and pubic hair, a deep voice, prominent muscles, and a large penis developed. There were no other complaints in a detailed systemic review, and there was no personality change. He continued to do well in school and appeared unconcerned with the changes occurring in the body.

The father, 28 years of age, and the mother, 31 years of age, were living and well; puberty for each of them had occurred between 12 and 13 years of age. A 17-month-old female sibling was normal. There were no deviations from normal in other kinships.

**Fig. 1.** Patient at time of first admission, aged 7 5/12 years.

The patient's birth and early development were normal. He had a tonsillectomy during the sixth year of life following rubella, rubeola, epidemic parotitis, and varicella, all of which occurred in rapid succession. There were no complications with any of these except bleeding which required a transfusion of blood following the tonsillectomy. There had been no unexplained fevers or central nervous system symptoms.

On admission, April 6, 1959, the height was 51½ inches, the weight, 72 pounds; the blood pressure, 105/60, and the pulse, 80 per minute. He was unusually developed and appeared to be both emotionally and intellectually older than the stated age of 7½ years (Fig. 1). There was acne over the face and back. There was no significant lymph node enlargement. The eyes, ears, nose, and throat were normal. Fundoscopic examination of the eyes were normal. The lungs, heart, and abdomen were normal. The pubic hair was gynecoid in distribution, and the penis measured 9 cm. in length. The testes appeared approximately normal in size for his age, and there were no abnormal masses palpable in the scrotum. Rectal examination revealed an easily palpable prostate which was thought to be definitely enlarged, but no fluid was produced on massage. Detailed neurological examination was within normal limits, and there was no intracranial bruit.

Laboratory data revealed a normal hemogram and urinalysis with specific gravity, 1.035; serum sodium, 142 mEq. per liter; potassium, 4.7 mEq. per liter; bicarbonate, 23.7 mEq. per liter; chlorides, 104 mEq. per liter; calcium, 5.1 mEq. per liter; phosphorus, 5.6 mg. per cent; blood urea nitrogen, 15 mg. per cent, and alkaline phosphatase, 23.8 Shinowara-Jones-Reinhart units. Twenty-four –hour urinary hormone determinations revealed: 17-hydroxycorticoids, 1 to 3 mg. (Porter and Silber); 17-ketosteroids, 3.2 to 5.5 mg.; pregnanetriol, 1 to 1.6 mg.; dehydroepiandrosterone, negative;* A-Z pregnancy test, positive; A-Z quantitative titer greater than 1,600 and less than 3,200 M.U. per liter. There was no suppression of the urinary 17-ketosteroids when 2 mg. of triamcinolone was administered 4 times daily for 6 days. Following administration of 40 units of ACTH twice a day for 2 days, there was a rise in urinary 17-hydroxycorticoids to 27 mg. per 24 hours. Visual fields were normal. Two electroencephalograms were reported to be normal. Excretory urograms and x-rays of skull, chest, and long bones were normal, and the bone age was estimated to be 9 to 10 years. Testicular biopsy showed hyperplasia of the spermatocytic precursors and the interstitial (Leydig) cells. There was an arrest of maturation at the secondary spermatocytic phase, and no mature sperms were found.

During the 2-month period of observation more body hair became apparent and face shaving was started. The testes ap-

*Courtesy of Dr. Cleveland, the Johns Hopkins Hospital.

peared larger than on admission and measured 3 cm. by 1½ cm. The patient remained asymptomatic. Various consultants added to the accumulation of data, but a specific diagnosis was not possible. In the absence of supporting evidence of intracranial disease, the neurosurgeon could not be persuaded to investigate the brain at this time. On the basis of the large amount of gonadotropin which was being excerted, a teratoma with placenta tissue (or choriocarcinoma) at an undetermined location in the body seemed likely. Therefore, on June 18, 1959, 6 months after virilism was first noted, a complete and careful abdominal exploration was carried out in search of a tumor. No tumor was located and the adrenals and periaortic nodes were found to be normal grossly and on microscopic examination.

Repeated and continued studies gave no positive clue of the source of the gonadotropins and in view of the negative abdominal exploration, pneumoencephalography and posterior fossa craniotomy were performed on Aug. 18, 1959. Although the initial study of the films suggested a possible mass in the third ventricle, as well as a possible mass in the occipital region, the latter was chosen for exploration because of its accessibility. The lower end of the vermis was split a short distance, and the cerebellar hemispheres were examined and retracted laterally which allowed the fourth ventricular floor to be seen, but no abnormality was visualized. Laminograms of the skull taken the following day appeared to show a soft tissue density on the roof of the third ventricle.

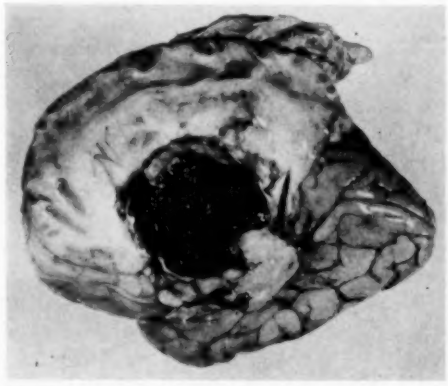


**Fig. 2.** Right parasagittal section of fresh brain, showing the large hemorrhagic neoplasm distending the third ventricle.

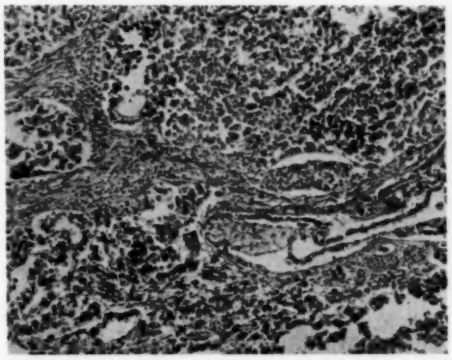


**Fig. 3.** Section of teratoma, showing variation in epithelial components, including several well-formed glands and one structure resembling sebaceous gland. (Hematoxylin and eosin stain. Original magnification ×110.)

Recovery from the foregoing procedure was surprisingly rapid, and the patient continued without signs or symptoms referable to the central nervous system. He did appear more masculine by photographic comparisons just prior to a second craniotomy with attempted exploration of the third ventricle on Oct. 20, 1959. Approach to the suspected tumor area through the corpus callosum was barred by large lesser veins of Galen. Underneath the 2 extremely large veins of Galen, the tissue appeared somewhat discolored, and the surgeon was certain that he was near a tumor, but he felt it unwise to proceed further.

Again recovery was smooth, and radiation therapy to the suspected tumor site was started; a total of 4,000 r. were given from Nov. 3, 1959, to Dec. 10, 1959.

For 3 months the boy did well at home, and then rather rapidly signs and symptoms of increased intracranial pressure developed with headache, vomiting, and bilateral papilledema. A palliative right ventriculoatrial

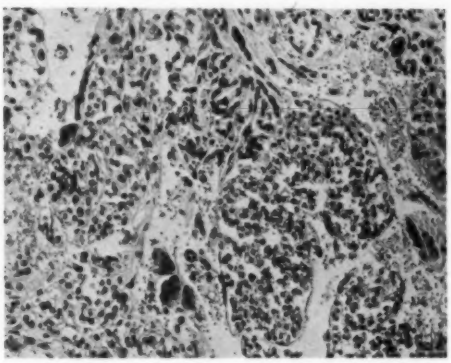


Fig. 4. Section of teratoma, showing area of choriocarcinoma with early degenerative changes; a retaining layer of syncytial cells still persists between the blood-containing sinuses and sheets of Langhans' cells. (Hematoxylin and eosin stain. Original magnification ×110.)

shunt was performed on March 19, 1960. The shunt appeared to function; however, his condition deteriorated progressively with increasing headache, lethargy, disorientation, coma, and rigidity. Terminally, he experienced a large gastrointestinal hemorrhage. He died on April 22, 1960, 12 months after the first admission to the hospital.

Although the results were available only after death, the very comprehensive assays* on the urine of March, 1960, are given as: ketosteroids, 9.6 mg. per day; pregnanediol, 8.76 mg. per day; estrogens, less than 1 R.U. per 100 ml. Gonadotropin levels were: (1) intact immature female rat, 100,000 R.U. per liter or 82,500 R.U. per day; (2) hypophysectomized female rat, negative at 0.1 to 50 ml. (at operation 21 days, assay 26 days, autopsy 30 days); (3) same as 2. Check for interstitial cell repair in ovaries, 10,000 units of interstitial-cell–stimulating hormone (ICSH) per liter; (4) hypophysectomized male rat, 10,000 to 20,000 units of ICSH per liter (ventral prostate and seminal vesicle tests); (5) constant estrus rat, 10,000 units of luteinizing hormone (LH) per liter (ovulation test); and (6) Weaver Finch (Paradise Wydah) test, 1,000 WFU of luteinizing hormone per liter.

Dr. Witachi commented that the analysis of the gonadotrophins showed only chorionic gonadotropin present. No response in the hypophysectomized female rat was interpreted as meaning complete absence of follicle-stimulating hormone. LH or ICSH was present as indicated by the check for interstitial cell repair in the ovaries of the hypophysectomized female rat, and the ventral prostate and seminal vesicle test in the hypophysectomized male rat. The ovulation test in constant estrus rats showed 10,000 units of LH per liter of urine. The Weaver Finch test was very helpful because it does not depend on any part of the genital system, but is a direct somatic reaction to LH.

*Courtesy of Drs. D. C. Johnson and Emil Witachi, University of Iowa, Iowa City.

## AUTOPSY FINDINGS

**Gross examination.** Autopsy was performed 12 hours after death. The general appearance of the body was that of a pubertal male of the age of 13 or 14 years, weighing 66 pounds, and measuring 60 inches in length. The skin of the upper back, face, and neck contained many acneform lesions. A heavy growth of hair was present on the extremities and in the pubic area, and there was a fine beard and mustache. Many healed surgical scars were present in the area of the head and neck, plus one old midline abdominal scar. The general muscular configuration was that of an adult male.

The peritoneal cavity, retroperitoneal area, and the contained organs were remarkable mainly for old adhesions and the surgical absence of the appendix and of the lateral pole of the right adrenal. The adrenals weighed 3.7 grams on the right and 5.4 grams on the left; they were otherwise normal. The liver contained no neoplasm on section, and search for neoplasm in the retroperitoneal lymph nodes was unrewarding. The source of the recent gastrointestinal bleeding was found to be a small duodenal ulcer, 3 mm. in diameter, on the posterior wall of the postbulbar area.

The right testis weighed 7 grams and

the left one 9 grams. The cut parenchymal surfaces were tan and slightly bulging, differing from normal adult parenchyma only in their less velvety appearance and in the failure of the tubules to string. Careful palpation and serial sections of each testis, creating sections 1 to 2 mm. in thickness, failed to reveal any foci of neoplasm or scars (other than that of biopsy). The prostate simulated that of a young adult in size and had a normal adult appearance on section. The seminal vesicles were well developed and contained mucinous tan fluid.

The heart, mediastinum, and neck were remarkable only for the presence of the unobstructed plastic tubing of the ventriculoatrial shunt subcutaneously in the right upper neck and scalp, and inside the right internal jugular and innominate veins, superior vena cava, and right atrial cavity. The lungs showed mild purulent bronchitis and foci of bronchopneumonia in both lower lobes, plus a small recent embolus in an arterial branch to the left lower lobe.

The brain was markedly and diffusely edematous, weighing 1,580 grams. Many adhesions in the areas of operations were encountered. The dural venous sinuses were normal. An old surgical tract through the cerebellar vermis ended in the fourth ventricle. The major finding was a large neoplasm measuring 6 by 5 by 6 cm., filling and distending the third ventricle and bulging through the dilated foramina of Monro to abut against the lateral walls of the greatly dilated lateral ventricles (Fig. 2). The neoplasm caused a downward displacement and effacement of the floor of the third ventricle. Demarcation of this mass from the surrounding brain was very sharp. The point of best attachment of neoplasm to the wall of the ventricle was in the posterior portion of the roof of the third ventricle. The neoplastic tissue was composed largely of hemorrhagic areas in its inferior half, while the dorsal and superior portions were soft, shaggy, and gray to white on section. An estimated 40 per cent of this mass was immediately removed, placed in a deep-freeze, and subsequently submitted to Dr. Johnson and Dr. Witachi for hormonal assays. The eluate obtained upon thawing the specimen gave positive tests for only chorionic gonadotropin. These assays paralleled the potency found in the urine. No attempt was made to analyze the hormone content separately of various portions of the tumor in relation to the microscopic appearance.

The pineal body was identified, posterior to and separate from the neoplasm. The pituitary was normal in all respects, although the infundibular stalk was shortened as a result of the downward displacement of the floor of the third ventricle.

**Microscopic examination.** Sections of the intracranial neoplasm presented the kaleidoscopic appearance of a malignant teratoma. Many areas were very poorly differentiated, with many bizarre cells and mitotic figures. Sarcomatous areas, e.g., leiomyosarcoma, were found, as well as epithelial structures resembling glands of the gastrointestinal tract, upper respiratory tract, and pilosebaceous apparatus (Fig. 3). Frequently, fields resembling embryonal carcinoma or seminoma of the testis were encountered. Most significant were large areas of unmistakable choriocarcinoma, with malignant syncytial trophoblasts interposed between blood-filled sinuses and sheets of malignant cytotrophoblasts (Fig. 4). Sections of the lateral walls of the third ventricle, after the neoplasm

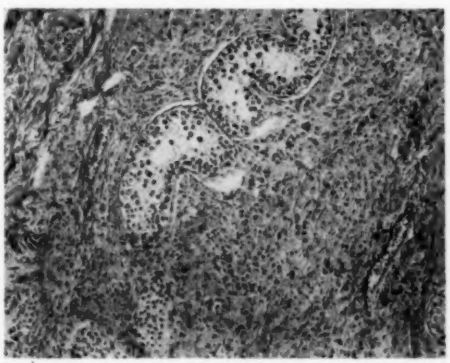


**Fig. 5.** Section of testis, showing diffuse hyperplasia of interstitial cells of Leydig. Seminiferous tubules of pubertal type. (Hematoxylin and eosin stain. Original magnification ×110.)

was bluntly separated from them, revealed no residual neoplasm. The sections from the posterior roof of the third ventricle showed small fingerlike extensions of neoplasm into the adjacent corpus callosum. The section of the separate pineal body revealed no neoplasm. The pituitary and adrenals were unremarkable except for old capsular and pericapsular fibrosis.

No neoplasm was identified in any of the viscera or lymph nodes. Multiple sections of both testes showed no microscopic neoplasm or foci of scarring other than in the area of the biopsy. The testes, however, were striking for the extreme diffuse increase in number of the interstitial cells of Leydig (Fig. 5). Nodules of Leydig cells were found even in the tunicae albugineae. The seminiferous tubules were well developed and contained normal spermatocytic precursors in great numbers, up to and including secondary spermatocytes, but only rare spermatids and no spermatozoa were present. The prostate and seminal vesicles had reached an adult stage of development.

## DISCUSSION

It is evident that an early diagnosis could not be established in this case. The relatively low excretion of 17-ketosteroids, the increase in size and demonstrated maturation of the testes on biopsy, and an excellent increase in urinary excretion of compound F after stimulation with ACTH suggested that we were not dealing with adrenal hyperplasia. The symmetrical growth of both testes, an early biopsy showing Leydig cells to be quite hyperplastic, and the lack of evidence of microscopic tumor was against the presence of any type of endocrine tumor of the testes. At that time there was nothing to indicate a hypothalamic lesion as the cause of the precocity. With the high concentration of gonadotropins one could only speculate that a secreting tumor, possibly teratoma with placental tissue, must be present some place in the body. With no further lead it seemed reasonable to surgically explore the patient's abdomen for such a tumor, but none was found. The procedure did, however, give an opportunity to observe the adrenals, which were grossly and microscopically normal. It then became clear that we had to look further for a tumor. On the basis of probability and with no indicative neurological findings, ventricular air studies were performed; they revealed what appeared to be a remarkably large brain tumor. Since the most common tumor responsible for the clinical pattern of the boy has been associated with the pineal body with a secondary influence on the pituitary, it was thought that such a lesion was the most likely one. Hormonal assays have definitely ruled out this possibility by the unequivocal demonstration that the large amount of gonadotropin in both the urine and the tumor eluate was of chorionic origin only.

Teratoma associated with precocious sexual development in the male is rare. One presacral teratoma containing androgen-producing tissue has been described in a 9-month-old male infant.[6] In this instance there appeared good evidence from the histologic picture and from demonstration of the hormone by bio-assay that the tumor did contain functioning adrenal cortical tissue. It has also been considered that a tumor arising from the pineal body may by virtue of its location cause precocity. There is, however, no evidence of hormonal studies to prove this concept. We think that we have adequate proof that the tumor found in our patient's brain was in itself responsible for the precocity and in this respect represents a unique and heretofore unpublished observation.

## SUMMARY

An instance of precocious puberty in a 7-year-old boy has been presented. After extensive study to exclude adrenal dysfunction, testicular tumor, and teratoma elsewhere in the body, a tumor of the third ventricle was found. The tumor was a teratoma and contained a secreting chorionepithelioma. Although it has been suggested that brain tumors may themselves secrete a hormone which influences sexual development,

no proof of this has been found in the literature and we believe in this respect our case is unique.

## REFERENCES

1. Wilkins, Lawson: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, ed. 2, Springfield, Ill., 1957, Charles C Thomas, Publisher, pp. 200-208.
2. David, M., Ajureaguerra, J. de, and Bonis, A.: Early Puberty Related to Cerebral Tumors, Semaine d. hôp. Paris **33:** 3935, 1957.
3. Weinberger, L. M., and Grant, F. C.: Precocious Puberty and Tumors of the Hypothalamus, Arch. Int. Med. **67:** 762, 1941.
4. Askanazy, M.: Chemische ursachen und morphologische wirkongen bei geschmulstkranken, insbesondere ueber sexuelle fruehreife, Ztschr. f. Krebsforsch. **9:** 393, 1910.
5. Stowell, R. E., Sachs, E., and Russell, W. O.: Primary Intracranial Chorionepithelioma With Metastases to the Lungs, Am. J. Path. **21:** 787, 1945.
6. Rhoden, A. E.: Precocious Sexual and Somatic Development in a Male Infant With Presacral Teratoma Containing Androgen-Producing Tissue, J. Clin. Endocrinol. **4:** 185, 1944.

# *Cebocephaly with endocrine dysgenesis*

## *Report of 3 cases*

**J. C. Haworth, M.D., M.R.C.P.,* Harry Medovy, M.D., F.R.C.P.(C), and A. J. Lewis, M.B., B.S.**

WINNIPEG, MANITOBA

THERE is a group of malformations involving the absence of the olfactory nerves and tracts and varying portions of the rhinencephalon (arhinencephaly) with abnormalities of the structures of the skull and face. The most severe of these malformations is cyclopia in which the orbits are fused and the nose is represented by a proboscis-like structure usually above the orbit. This condition is fortunately not compatible with life. In other types of arhinencephaly, while there may be malformations of the nose, lips, and palate, the orbits are separate but may be set abnormally close together (hypotelorism). One variety has been called cebocephaly (monkey head) because the rudimentary nose recalls that of the platyrrhine monkeys. This monstrosity was apparently first described by Geoffrey St. Hilaire in 1836. In a search of the literature of the past 44 years, we have been able to find reports of only 2 cases of cebocephaly[1, 2] although there is brief reference to another case by Yakovlev,[3] and Potter[4] shows illustrations of 2 cases but no details are given. One other case report is listed but the original article is not available to us.[5] Within the past 6 months we have seen 2 examples of this malformation and have been able to obtain details of a third case. We are aware of 2 other cases which have not been published so far; there may be others. In view of the apparent infrequency of the condition and because 2 of our cases showed abnormalities of the endocrine system we think the following report may be of interest.

*From the Children's Hospital, Winnipeg, and The Department of Paediatrics, University of Manitoba.*

**Address, The Winnipeg Clinic, Winnipeg 1, Manitoba.*

### CASE 1

This baby girl was born after a 38 weeks' gestation. The birth weight was 6 pounds (2,720 grams); length was 17¼ inch (43.8 cm.). The mother was a mentally deficient, unmarried girl, aged 28 years. For obvious reasons it was difficult to obtain an accurate prenatal history, especially with regard to the possibility of the use of abortifacients in early pregnancy. There was no history of maternal bleeding during pregnancy. The baby's breathing, color, and tone were very poor at birth, and an Apgar rating of 3 was assigned 60 seconds after birth.

The infant was grossly malformed (Fig. 1). The face and head of the infant presented a grotesque appearance. The head was small with a receding forehead, eyes placed close together, and a proboscis-like structure representing the nose was situated in the midline. The head circumference was 11¾ inches (29.8 cm.). The anterior fontanel was small, admitting the tip of one finger. The posterior fontanel measured 2.5 by 1 cm. Both pupils were small and central, but the right did not react to light. The fundi were normal. The structure representing the nose had a single opening with no septum. There was complete obstruction of the single choanal passage as determined by inability to pass an 8 F catheter more than 1 cm. and later by obstruction to the entrance of instilled Dionosil as shown by radiography. The palate was long, narrow, and almost flat with several anteroposterior grooves. The feet were inverted and the toes dorsiflexed. Fingers and toes appeared to be longer than normal. The baby was markedly hypotonic with a poorly sustained Moro reflex. Normal female genitals were present. Physical examination was not otherwise remarkable.

The infant had considerable difficulty with respiration, requiring a tracheotomy for relief. Respirations continued to be irregular. Moderately severe icterus became evident at 12 hours. She died when 72 hours of age.

**Laboratory findings.** A radiograph of the chest showed no significant abnormalities and the heart size was normal. A radiograph of the skull showed a small cranium and a rather shallow sella turcica with ill-defined anterior clinoid processes. The hemoglobin level was 20 mg. per 100 ml. The white cell count and differential were within normal limits. The serum bilirubin at 48 hours of age was 16.5 mg. per 100 ml. (direct 1.7 mg. per 100 ml.). The direct Coombs test was negative. The blood group was A, Rh positive. The urine contained albumin, 75 mg. per 100 ml., but was otherwise normal. Chromatin-positive cells were present in a buccal smear. A bone marrow aspiration after colcemid administration showed a normal chromosome count and morphology.

**Autopsy.** The vault of the skull showed marked overriding of bones and the anterior fontanel was small (15 by 12 mm.). The metopic suture was almost closed. No falx cerebri was present and the superior sagittal sinus was rudimentary. Structurally the meninges were normal except at the base of the forebrain where they were thickened and inseparable from the brain. The configuration of the dural sinuses was not unusual.

The brain weighed 150 Gm. (normal 300 to 350 grams) and showed fused frontal lobes and rather poorly demarcated temporal poles. The superior frontal, parietal, and occipital regions were absent, leaving a free edge of hemispheral substance which was crescentic and fused at its extremities with the floor of the cerebrum lateral to a median mass. Beneath this free edge was a semidiscoid space representing the fused lateral and third ventricles. This space communicated by an opening 5 by 4 cm., defined by the free edge, with a cystic space occupying the rest of the vault (Fig. 2).

In the base of the forebrain, below the crescentic opening, lay a median mass about 2.5 by 3 cm., with a poorly marked median groove terminating posteriorly in the aqueduct. On either side, laterally and parallel to the median groove, ran a small ridge to which were attached brownish tags of choroid plexus. The basal ganglia could not be identified. The lining of the fused ventricle and of that part of the median mass between the lateral ridges as far back as the aqueduct was ependymal. Lateral to these ridges pia-arachnoid covered the mass and was continuous laterally with that covering the cerebrum and posteriorly with that covering the tentorium and forming part of the cyst wall.

The leptomeninx split at a level about 2 cm. outside the crescentic margin. Outside this a single layer descended on the external cerebral surface. Inside, the lowest layer descended over a rather smooth nonconvoluted surface to join ependyma at the

**Fig. 1.** Faces of Cases 1, 2, and 3 (from left to right).

free edge; the uppermost layer lined the dura to form the wall of the cyst in the vault. Neural material was not identified in this wall which appeared entirely meningeal.

The base of the forebrain, anterior to the pons, was a mass of firm grey tissue, largely formed by the meninges which could not be stripped away. From this mass emerged the optic and oculomotor nerves. It was entered by the internal carotid arteries and from it issued the anterior and middle cerebral branches, the latter small and supplying the posterior quarter of the ventral cerebral surface and part of the cyst wall. No infundibulum was seen, and the pituitary gland was absent. No olfactory nerves, bulbs, tracts, or striae were seen. The cerebral convolutions were quite unlike those of the normal brain.

The form of the brain stem and cerebellum was fairly normal. The corpora quadrigemina were partially fused to form a single mass. The pons was small. Pyramids were absent from the ventral medullary surface and no decussation was observed. With the exception of the olfactory nerve the cranial nerves were all present. The basilar artery branched normally, the posterior cerebral branches being small and supplying the cyst wall. The spinal cord appeared within normal limits and the spinal nerves were normal.

Gross sectioning of the cerebrum showed poor differentiation of white from grey matter. The median mass was composed of grey matter, presumably thalamic in nature and no evidence of basal ganglia was seen. No internal structure was discerned in the midbrain but the pons, cerebellum, and medulla appeared normal apart from the absence of pyramids. Sections of the cord showed small lateral columns.

In the base of the skull there was no pituitary fossa or sellar diaphragm. The posterior clinoid processes were partly fused to a single mass and the anterior were rudimentary. There was no crista galli and the cribriform plates were represented by shallow smooth depressions. The greater sphenoid wing was underdeveloped and the anterior and middle fossae were not sharply delimited.

A probe could be passed only about 1 cm. into the nostril. Studies of this area, which are continuing, showed an absence of nasal septum structures (i.e., septal cartilage, vomer, and median ridges of palatine and palatine processes of maxillary bones). The anterior ossification center of the body of the sphenoid was maldeveloped, the orbital plates were fused in the midline, and there was fusion of the body of the sphenoid and hard palate. The anterior nostril was full of fatty tissue and no respiratory or olfactory

epithelium could be shown. The posterior choana, soft palate, uvula, and pharyngotympanic tubes appeared fairly well formed.

Permission was not obtained for removal of the eyes.

The adrenal glands were small, weighing together about 0.5 gram (normal 4 to 5 grams). They were approximately equal in size and normal in shape. The cut surface showed no lamination. Histologically they showed no fetal cortex and were made up of small lobules of polygonal cells with pale cytoplasm, separated by strands of fibrous tissue (Fig. 3). The smallest of these clumps resembled tubules. There was extreme cytoplasmic vacuolation except at the edges of the glands, where the cytoplasm was less vacuolated and showed some amphophilia.

The thyroid gland weighed 0.46 gram (normal 0.8 to 1.1 grams) and was normal in shape. The lobules were small and separated by fibrous strands. They were composed of irregular acini lined by very flat cells and containing extremely pale colloid (Fig. 4). These changes seemed to be an exaggeration of the immaturity seen in normal premature infants.

Serial sections were made in the region of the pituitary fossa and no pituitary tissue was found. Other endocrine tissues were grossly and histologically normal.

The spleen weighed 14 grams and was fissured; there was a small accessory spleen.

The lungs showed areas of atelectasis with moderate edema and shedding of septal cells.

No gross or histologic abnormalities were seen in other organs.

**CASE 2**

This baby girl was born in a country hospital. The mother had had polyhydramnios during her pregnancy and the baby was born following artificial rupture of the membranes. The father was 30 years old; the mother 27 years and both were healthy. There were 3 older normal children including twins. The baby was noted to be abnormal at birth, was cyanosed, and in respiratory distress. An oral pharyngeal airway was inserted and the baby was transferred to the Children's Hospital, Winnipeg, when 24 hours old.

On examination the baby's general condition was fairly good and she was breathing easily through the airway. She weighed 6 pounds, 4 ounces (2.8 kilogram) and was 20 inches (51.8 cm.) in length. The head appeared small and was only 11¾ inches (29.8 cm.) in circumference. The anterior fontanel was patent but small. The facial appearance was striking (Fig. 1). The orbits were set close together and the eyes were small, making examination of the fundi unsatisfactory. The nose was rudimentary and contained a single nostril through which it was impossible to pass a small catheter (5 F). The palate appeared abnormally narrow. She cried fairly normally but exhibited a poor Moro reflex and no grasp reflex could be obtained. The external

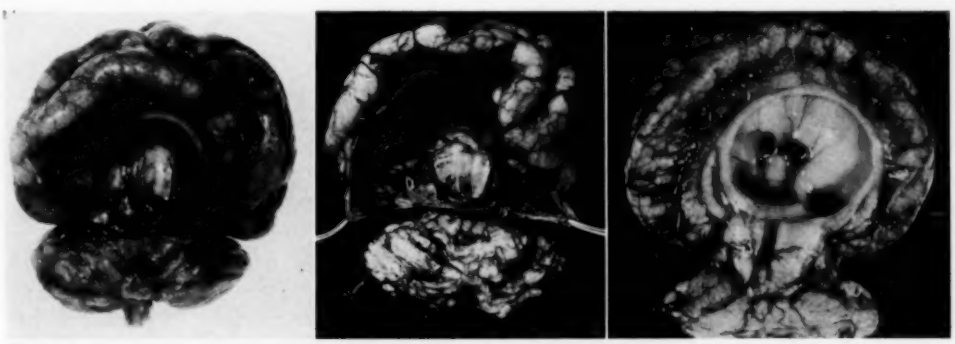


**Fig. 2.** Dorsal views of the brains of Cases 1, 2, and 3 (from left to right), showing the absence of parietal and occipital cortex and looking down into the single ventricles.

genitals were those of a normal female infant. No abnormalities were detected in the lungs, heart, or abdomen.

The baby became very distressed and cyanotic when the airway was removed. The presence of choanal atresia was confirmed by radiography with the use of contrast medium. The nose was then examined under anesthesia, and it was found that operation was not feasible. A tracheotomy was performed. Thereafter, the baby's condition remained fairly good except that she was limp and unresponsive. Because there was no sucking reflex, she was fed by gavage.

**Laboratory findings.** At 4 days of age, the hemoglobin level was 21.7 Gm. per 100 ml.; urine, normal; serum bicarbonate 16 mEq. per liter, sodium 139 mEq. per liter, potassium 6.0 mEq. per liter, and chlorides 116 mEq. per liter.

At 2 weeks of age the serum bicarbonate was 20 mEq. per liter, sodium 129 mEq. per liter, potassium 6.4 mEq. per liter, and chloride 100 mEq. per liter.

Oral glucose tolerance test showed fasting blood sugar level 62 mg. per 100 ml., ½ hour, 125; 1 hour, 47; 2 hours, 46; 3 hours, 43 mg. per 100 ml.

17-Ketosteroid excretion was 1.62 mg. per 24 hours. 17-Ketogenic steroid excretion was 1.73 mg. per 24 hours. Protein bound iodine 7 μg per 100 ml.

Radiographs of the skull showed a small cranium, both orbits appeared very close together and at one point were only 4.5 mm. apart. (This is well below the normal range.[6]) The ethmoids and nasal bones were poorly developed but the other facial bones were reasonably well formed. The sella turcica appeared normal. A radiograph of the chest was normal.

**Further course in hospital.** During the 3 months the baby was in the hospital she lay limp and unresponsive although she would cry when stimulated. She never seemed to be aware of her surroundings. During the last month she had an increasing number of minor motor seizures and episodes of apnea and cyanosis. She died quite suddenly at the age of 14 weeks without exhibiting any signs of an infection.

**Autopsy.** The vault of the skull was small with overriding bones and an anterior fontanel measuring only 14 by 6 mm. The metopic suture was almost closed.

The development and configuration of the dura and leptomeninges were almost identical with those in Case 1, except that the basal thickening of the pia-arachnoid was less marked.

The brain weighed 155 grams (normal 475 to 525 grams) and closely resembled that of the preceding case (Figs. 2 and 5). There were, however, 2 small projections just anterior to the median mass which probably represented the heads of the caudate nuclei. The convolutional pattern differed from that of Case 1 but was still not

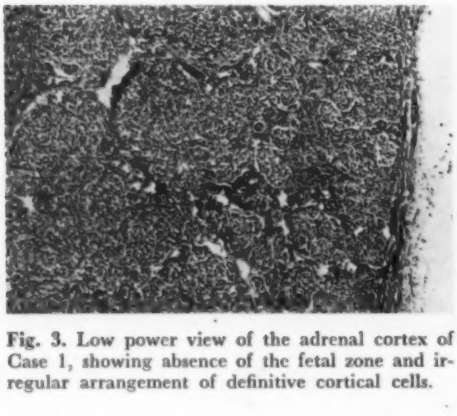


**Fig. 3.** Low power view of the adrenal cortex of Case 1, showing absence of the fetal zone and irregular arrangement of definitive cortical cells.

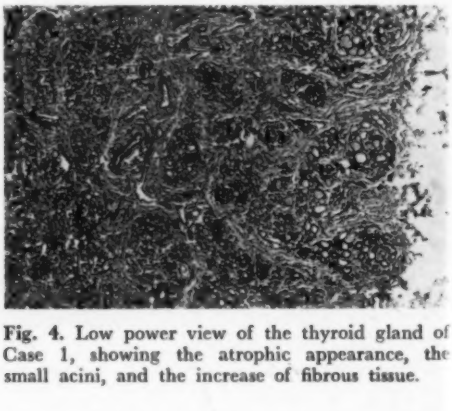


**Fig. 4.** Low power view of the thyroid gland of Case 1, showing the atrophic appearance, the small acini, and the increase of fibrous tissue.

normal. A pituitary gland of normal size, shape, and color was present. The spinal cord appeared grossly normal.

The base of the skull showed a shallow pituitary fossa, and the anterior and posterior clinoid processes were well developed. No sellar diaphragm was noted. In other respects the base of the skull was the same as in Case 1.

A probe could be passed only about 8 mm. into the nostril and preliminary examination of the nasal region showed the same defects as in the preceding case.

The endocrine glands appeared normal. The adrenal glands weighed 1,590 and 1,875 milligrams and the thyroid 1,280 milligrams, figures which are within the wide normal range. Histologically no abnormalities were seen.

The lungs weighed 60 and 55 grams (normal about 40 and 35 grams). Several firm, dark red areas were noted. Histologically these showed small foci of parenchymal necrosis, necrotizing bronchiolitis, and intranuclear inclusions typical of adenovirus infection.[7]

The spleen weighed 28 grams and there was a single large fissure near the lower pole on the medial aspect.

No gross or histologic abnormalities were seen in other organs.

### CASE 3

This was a premature, Negro male infant who was born after a normal pregnancy and delivery to a healthy 19-year-old mother. This was her first child. The placenta weighed 355 grams. At birth the baby did not breathe for 50 seconds and resuscitation with endotracheal intubation was necessary. The baby remained cyanosed and in respiratory distress and an emergency tracheotomy was performed.

On examination the baby was noticed to have a malformation of the nose with a single nostril (Fig. 1). There were supernumerary digits on both hands and feet. He was nursed in oxygen with high humidity and given penicillin and streptomycin. During the first 48 hours of life no

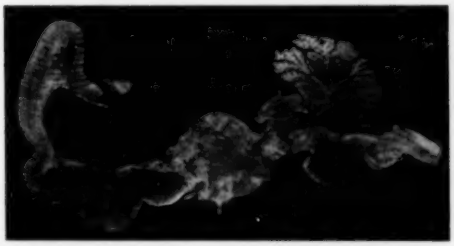


Fig. 5. Sagittal section of the brain of Case 2.

stools were passed. A barium enema was performed and showed narrowing of the distal colon. There was partial obstruction of this area from multiple meconium masses with moderate distention of the large and small bowel proximally. Following the barium enema the baby had a bowel movement.

On the fourth day of life marked jaundice appeared (total bilirubin 16.8 mg. per 100 ml.). The child became lethargic, râles appeared at both lung bases, respiratory difficulty increased, and the baby died at the age of 5 days.

**Additional laboratory findings.** The hemoglobin level was 12.3 Gm. per 100 ml. Blood culture was sterile. The urine was normal.

**Autopsy.** The body weighed 1,825 grams and measured 47 cm. in length. The brain weighed 92 grams (Fig. 2) (normal 325 to 375 grams). The hemispheres were fused and were of doughnut shape, surrounding a central opening 3.5 cm. in diameter. This opening communicated with a fused ventricle, on the posteroinferior aspects of which 2 choroid plexuses were present. No gyral pattern was apparent. The cerebral peduncles and cerebellum were displaced posteriorly. The foramen magnum was flattened anteroposteriorly and narrowed. The septum pellucidum and corpus callosum were absent. The base of the brain showed no olfactory tracts or bulbs.

The palate showed a slightly elevated central raphe, on either side of which were 2 deep grooves extending the entire length of the hard palate. There was no communication between the grooves and the nasal

cavity. There was a single posterior choana communicating with the pharynx.

The pituitary gland was not present. The 2 adrenal glands together weighed 2.1 grams and showed a yellowish tan cortex somewhat reduced in thickness. Histologically, the fetal cortex was very thin. The zona glomerulosa was thicker than normal and the general architecture was reminiscent of that seen in anencephalic monsters.

The thyroid was grossly normal. Sections showed diffuse congestion with well-developed acini containing eosinophilic colloid.

Testes were found at the internal inguinal rings and showed only some congestion and edema of the interstitial tissue.

The heart weighed only 6.3 grams but there were no structural anomalies. The lungs together weighed 52 grams and showed congestion and firmness. They did not float in water. The bronchi contained yellowish, slightly hemorrhagic mucoid material. Histologically there were edema, atelectasis, pyogenic bronchopneumonia, and aspiration.

The liver weighed 92 grams and was grossly congested. Histologically the only feature was dilatation of the central vein and capillaries.

There were no significant findings in other viscera.

## DISCUSSION

The appearance of the faces and heads of these 3 babies was almost identical as may be seen in Fig. 1 and also very similar to the illustrations of other cases that have been described.[1-4] The malformation of the brain in all 3 cases was also similar (Fig. 2). Case 3 had polydactyly and an incomplete cleft palate, abnormal features not seen in the other 2 cases. Potter[4] mentions that a rudimentary sixth digit is almost always found in cebocephaly. The case reported by Reventos[2] showed this abnormality but our Cases 1 and 2 and de Lange's[1] case did not. De Lange's case in addition showed colobomata of the irides, malformation of the thoracic vertebrae, and a patent ductus arteriosus. Reventos also described a single ventricle, double uterus and vagina, and eye abnormalities. None of these features were found in our 3 cases, although we did not obtain permission to examine the eyes at autopsy.

In Case 1, no pituitary gland could be found and there was absence of the fetal cortex of the adrenals. The thyroid gland also appeared hypoplastic. The pituitary and other endocrine glands appeared normal in Case 2. The pituitary gland was also absent in Case 3 and the fetal adrenal cortex was abnormally thin. A limited investigation of endocrine function was performed in Case 2 in view of the autopsy findings in Case 1. 17-keto steroid and 17-ketogenic steroid urinary excretion was within the normal range for age, and the protein bound iodine was also normal. The sella turcica appeared normal by radiograph examination and the serum electrolytes, although not entirely normal, did not suggest adrenal hypofunction. The oral glucose tolerance test showed a rapid rise and fall of blood sugar, a finding difficult to evaluate. The abnormal brain of this child was doubtless incompatible with lengthy survival but it is unlikely that she would have lived 14 weeks had the pituitary been absent as in Case 1. Infants born with absence of the pituitary and hypoplastic adrenal glands apparently die within a few hours of birth even if there is no associated gross congenital abnormality.[8-10]

Yakovlev[3] described absence of the pituitary in several cases of arhinencephaly. Edmonds[11] could find no sign of pituitary glandular tissue in 3 out of 5 cases of the closely allied condition of cyclopia. These 3 cases also showed reduction of the adrenal cortex and small thyroid glands. Anencephaly is another condition in which the adrenals are hypoplastic due to the absence of the fetal cortex. Angevine[12] showed that some pituitary anterior lobe tissue could always be found in this condition although he thought it was probably functionless. This observation is supported by the fact that if an anencephalic monster is given adrenocorticotropic hormone (ACTH) be-

fore death the adrenals at autopsy resemble those of a normal newborn infant.[13] The function of the fetal zone of the adrenal cortex, the mechanism of its rapid degeneration after birth, and whether it is under control of the fetal pituitary, the maternal pituitary, or the chorionic gonadotropins have been subjects for discussion for many years. Lanman[13] recently reviewed the evidence and considered that ACTH from the fetal pituitary is the tropic hormone inducing the hypertrophy and hyperplasia of the fetal zone. We do not feel that our limited observations can add anything in this regard.

We do not propose to discuss the etiology of cebocephaly and related monstrosities in this paper, except to note that the most probable cause is some unknown noxious influence acting on the fetus during the first few weeks of development. Cyclopia, for instance, has been artificially produced by a number of factors during the early embryonic development of fishes.[14, 15] There is no evidence for any genetic cause for this group of malformations and our studies in Case 1 appear to exclude any visible chromosome abnormality. A more detailed pathologic report of these 3 cases with further discussion of the etiology will appear later.[16]

## SUMMARY

Three cases of cebocephaly are reported. This malformation differs from the closely allied condition of cyclopia in that the orbits are separate, although showing hypotelorism, and there is a rudimentary nose with a single nostril in the normal position. The brains of the 3 cases showed the almost identical malformation of arhinencephaly.

Two cases were found to have absence of the pituitary gland and hypoplasia of the adrenal cortex and in addition one showed hypoplasia of the thyroid gland. The endocrine system of the third case was apparently normal. Chromosome counts in one case were normal.

We are very grateful to Dr. Heyworth N. Sanford of the Infant Research and Education Hospital, University of Illinois, for permission to publish Case 3 and to Dr. Vera Gellman for help with the details of this case. We also thank Dr. Irene Uchida for the chromosome analysis of Case 1, Dr. A. E. Childe for the radiographic reports, Dr. J. Hoogstraten for the photomicrographs, and Mr. Tony Gibson for the photographs.

## REFERENCES

1. deLange, C.: Cebocephalia Minor, Acta psychiat. et neurol. **15:** 299, 1940.
2. Reventos, J. D.: Estudio de un cebocefalo nacido vivo de un embarazo hidramniotico, Rev. Espan. Obst. Valencia **17:** 188, 1958.
3. Yakovlev, P. I.: Pathoarchitectonic Studies of Cerebral Malformations. 111 Arrhinencephalies (Holotelencephalies), J. Neuropath. & Exper. Neurol. **18:** 22, 1959.
4. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, 1952, Year Book Publishers Inc., p. 421.
5. Ito, M., Sono, T.: Ein Seltener Fall Von Cebocephalie, Oto-rhino-laryng. **11:** 319, 1938.
6. Currarino, G., Silverman, F. N.: Orbital Hypotelorism, Arhinencephaly, and Trigonocephaly, Radiology **74:** 206, 1960.
7. Hoogstraten, J., Lewis, A. J., Parker, W., Young, G.: Fatal Adenovirus Pneumonitis in Infants (to be published).
8. Blizzard, R. M., Alberts, M.: Hypopituitarism, Hypoadrenalism, and Hypogonadism in the Newborn Infant, J. PEDIAT. **48:** 782, 1956.
9. Brewer, D. B.: Congenital Absence of the Pituitary Gland and Its Consequences, J. Path. Bact. **73:** 59, 1957.
10. Reid, J. P.: Congenital Absence of the Pituitary Gland, J. PEDIAT. **56:** 658, 1960.
11. Edmonds, H. W.: Pituitary, Adrenal and Thyroid in Cyclopia, Arch. Path. **50:** 727, 1950.
12. Angevine, D. M.: Pathologic Anatomy of Hypophysis and Adrenals in Anencephaly, Arch. Path. **26:** 507, 1938.
13. Lanman, J. T.: The Adrenal Gland in the Human Fetus, Pediatrics **27:** 140, 1961.
14. Stockard, C. R.: The Artificial Production of One-Eyed Monsters and Other Defects, Which Occur in Nature, by the Use of Chemicals, Anat. Rec. **3:** 167, 1909.
15. Lewis, W. H.: The Experimental Production of Cyclopia in the Fish Embryo (Fundulus Heteroclitus), Anat. Rec. **3:** 175, 1909.
16. Lewis, A. J.: The Structural Anomalies in Cebocephaly (in preparation).

# *Symposium on adolescence: Introduction*

**Waldo E. Nelson, M.D.***

PHILADELPHIA, PA.

IF ONE thinks of adolescence in terms of an explosive phenomenon or, for those perhaps more aesthetically inclined, as the unfolding of the flower from the bud to the full bloom, then one sets out to determine the ranges of normalcy: the time of detonation, too early or too late; the strength of the reaction, too weak or too violent; and the appropriateness of the environment, too much or too little of many variables.

As in other age groups, physical health during the adolescent period, as measured by the incidence of serious morbidity and by mortality rates, has been greatly improved in recent years. This general improvement does not lessen the need, however, for more thorough investigation of the patterns of disease in the adolescent and of their effects on his development. As is the case in infancy, the other of the 2 postnatal growth spurts, reactions to disease are often altered in relation to the metabolic activity; in general they tend to be more violent than in periods of lesser or no-growth activity. Thus the adolescent period provides many opportunities for research directed at a better understanding of disease processes.

The situation in regard to mental and emotional health is even less clear. Increased attention to behavioral patterns and to mental illness might suggest that there has been an increased incidence of emotional disturbances among adolescents. The seriousness of the delinquency problem, especially in our large cities, tends to support such an assumption. However, there are inadequate data to indicate the relative incidence of frequency of behavioral disorders during adolescence at the present time, in comparison with past years. Without failing to recognize that this area represents one of our principal challenges at the moment, it would seem, at least to me, that reasons for optimism concerning the dependability of our youth far outweigh those for pessimism. But we must learn more about the adolescent and, in particular, about his environmental medium.

In a very real sense, the outstanding problem of the adolescent is the adult. If the

*The papers here presented in abbreviated form constituted the academic program for the first A. Graeme Mitchell Memorial Day in Cincinnati, Feb. 22, 1961. Under the leadership of Dr. Carl Ochs, former pupils, colleagues, and friends of Dr. Mitchell have created a memorial fund which will be used to aid the Department of Pediatrics at Cincinnati, especially in respect to activities related to the adolescent.*

*This Symposium was supported in part by a grant from The Merck Sharp & Dohme Postgraduate Program.*

**Address, St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pa.*

physician can help the parent to be understanding of the child through the various phases of his growth, he will have made a considerable contribution to lessening the disturbances of the adolescent period. Similarly the physician has the opportunity to help the child to an understanding of the adult and of his (the child's) responsibilities in family living.

The question is often asked: Which category of physician should assume responsibility for the medical care of the adolescent? Should the adolescent be the medical responsibility of the pediatrician, the internist, the general practitioner, or should we develop a new category, termed perhaps the adolestician? I suspect most of us would speak strongly against the last possibility. The adolescent might well receive continuing medical supervision by a physician in any of the first 3 categories, provided that the physician was interested in the adolescent and would give sufficient time to deal with his problems. In taking a stand against the creation of a new medical specialty for the adolescent age group, we do support the segregation of interests by a few physicians in the field of adolescence. Such medical personnel would in most instances be most appropriately located in medical schools. Certainly there is a need for medical activities related to the adolescent, such as those which are represented by the interests of our panel members. Essential for the physician who proposes to provide medical guidance for adolescents are a deep interest in young people, a knowledge of their medical problems, an ability to provide counseling service, and a willingness to give the time required. Pediatrics has as its goal the guidance of its patients through the several phases of growth and development in such a manner that they attain adulthood at something approaching their respective optimal capacities. The pediatrician should be especially fitted to continue medical supervision through adolescence. In many instances, he is.

# *Secular acceleration of height and biologic maturation in children during the past century*

**Thomas E. Cone, Jr., Captain (MC) USN***

CHILDREN in the United States and in Western Europe are not only growing taller in successive generations but are also reaching biologic maturity at an earlier age.[1-5] This secular acceleration of statural size and biologic maturation has been evident during the past century and there is as yet no proof that these accelerative trends are slowing down. An appreciation of these biologic variables is of importance for those interested in human growth and development as well as for the clinician concerned with the routine health evaluation of children. Tanner[6] has collated growth data from many countries to point out that this trend is not limited to any one country or area. It would be reasonable to assume that the continuous lowering of the age of adolescence will produce sociologic as well as medical effects.

## SECULAR ACCELERATION IN HEIGHT

Franz Boas,[7] the great physical anthropologist, over 30 years ago, took issue with 2 generally accepted assumptions concerning the growth of children. These were that the physical traits of the population represented by children of different ages remain the same from year to year and that all children pass through the periods of more rapid growth from birth to maturity at the same time. His observations showed further that from the middle of the past century the average stature of children in Europe increased in each country and that the statural increase was so significant that it could not be explained statistically by accidental causes alone.

The acceleration in the rate of growth probably started about a century ago. In 1876, Roberts[8] stated that the average factory child at the age of 9 weighed as much as one of 10 years had in 1833 and that there had been comparable gains in children at all ages of childhood beyond infancy during this period of 43 years. Kiil's[9] review of the growth in stature of Norwegian men during the past 200 years would also suggest that the present accelerative phase began about 1830 to 1840.

A curious and unexplained disinterest in physical growth and biologic maturation existed among physicians until relatively recently. The great Greek, Roman, and Arabian physicians apparently never described, or at least never mentioned, a single observation of human growth in terms of

*From the Pediatric Service, United States Naval Hospital, Bethesda, Md.*

*The opinions or assertions contained in this article are the private ones of the writer and are not to be construed as official or as reflecting those of the Navy Department or the Naval Service at large.*

**Address, United States Naval Hospital, Bethesda 14, Md.*

definite units of measurement in any of their medical writings.[10]

Not until 1835 did the first accurate study of human growth from birth to maturity appear.[11] The author of this study was a Belgian astronomer and statistician named Quetelet to whom all physicians owe a debt of gratitude for creating the foundation upon which subsequent studies of human growth and development are based. Table I, which lists Quetelet's measurements of the heights of Belgian children from birth until 18 years of age, is of historic as well as of practical value. His table depicts sophistication in the presentation of growth data; it provides not only the maximum and minimum limits of growth for each sex, but also the increments of growth per year. These latter measurements reflecting the rate of growth per unit of time were not previously mentioned by any writer with the possible exception of the Count de Montbeillard,[12] who measured a single individual—his son from 1759 to 1777.

It was not until 1877 that there were growth data for children in the United States approximating those of Quetelet.[13] Comparable data of statural growth of British children did not appear until 1883.[14]

The secular trend for boys and girls in the United States is depicted in Figs. 1*A* and 1*B*. These figures compare the median heights of Boston school children measured by Bowditch[13] in 1877 with those living in the same city and of similar ancestry measured by Reed and Stuart[15] during the years 1930 to 1956 as one objective of the project known as the "Longitudinal Studies of Child Health and Development of the Harvard School of Public Health."

It is realized that in comparing Bowditch's measurements with those of Stuart, one is contrasting the former investigator's cross-sectional data with the longitudinal studies of the latter workers. However, merely for the depiction of secular trends the use of these 2 different types of growth data would not seem too indefensible.

Figs. 2*A* and 2*B* show that the same secular trend has occurred in Great Britain since 1883. It was in this year that one of the earliest cross-sectional growth studies was performed by the British Anthropometric Committee.[14] The average height values of British boys and girls measured in 1883 are noted to be considerably less than those measured in 1947.[1]

Fig. 3 shows that London schoolboys measured over a period of 45 years have continued to grow progressively taller during this period of time. In fact, the average height of these schoolboys has increased by about 7.5 cm. (3 inches). Figures from

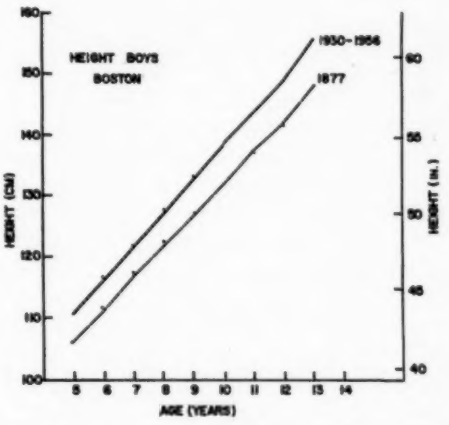



**Fig. 1*A*.** Increase in mean stature of Boston boys measured in 1877 and during the years 1930 to 1956.

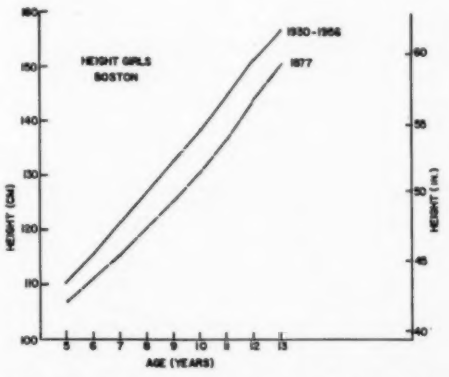



**Fig. 1*B*.** Increase in mean stature of Boston girls measured in 1877 and during the years 1930 to 1956.

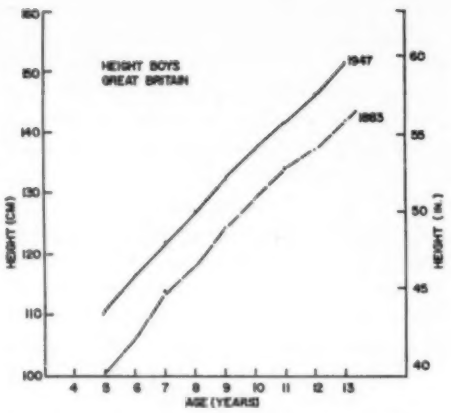



**Fig. 2*A*.** Secular trend in height of boys in Great Britain measured in 1883 and in 1947.

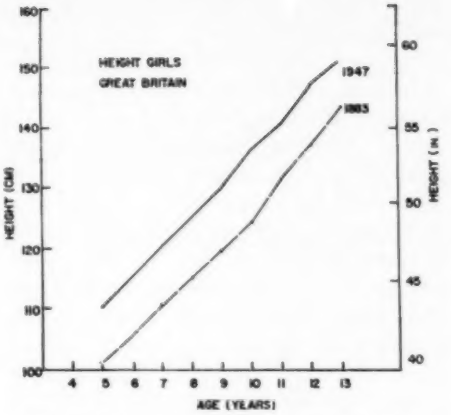



**Fig. 2*B*.** Secular trend in height of girls in Great Britain measured in 1883 and in 1947.

Glasgow of the growth in height of schoolboys of comparable ages during this same span of years demonstrate a similar secular trend.[2]

Fig. 4 shows the striking increase of height of English prep school boys of 1959 in comparison with their counterparts of 1944. During this short period of time the height of the 11-year-old boy increased 2 inches; that of the 12-year-old boy, 2¾ inches, and that of the boy of 13 years, 2½ inches.[16]

Further evidence that this is a real accelerative growth trend rather than a juggling of unrelated samples and comparisons comes from the anthropometric studies from many American colleges and universities. In general, these studies have been based upon the entrance physical examinations of students. Those reports which have received careful analytic study call attention to the secular changes taking place in this segment of the American population. By comparing year after year the dimensions of students of the same age, it is apparent that the height of students is gradually increasing.[17]

The reasons for this secular change in growth are not certain. Better nutrition, the improvement of the standard of living, the control of many serious diseases of childhood, and the ever-widening dissemination of in-

**Table I.** Averages and ranges of heights of boys and girls of Belgium in year or years (Adapted from Quetelet)

| *Ages (years)* | *Height of boys (M.)* | *Range* | | *Height of girls (M.)* | *Range* | | *Range of differences of height* | | *Average differences (M.)* |
|---|---|---|---|---|---|---|---|---|---|
| | | *Maximum (M.)* | *Minimum (M.)* | | *Maximum (M.)* | *Minimum (M.)* | *Boys (M.)* | *Girls (M.)* | |
| Birth | 0.491 | 0.588 | 0.458 | 0.491 | 0.520 | 0.452 | 0.130 | 0.068 | 0.099 |
| 0 to 1 | 0.620 | 0.688 | 0.504 | 0.620 | 0.695 | 0.570 | 0.184 | 0.125 | 0.154 |
| 1 to 3 | 0.792 | 0.883 | 0.680 | 0.780 | 0.862 | 0.664 | 0.203 | 0.198 | 0.200 |
| 3 to 5 | 0.947 | 1.011 | 0.882 | 0.898 | 1.027 | 0.822 | 0.129 | 0.205 | 0.167 |
| 5 to 7 | 1.050 | 1.139 | 0.927 | 1.030 | 1.150 | 0.958 | 0.212 | 0.192 | 0.202 |
| 7 to 9 | 1.176 | 1.215 | 1.150 | 1.112 | 1.186 | 1.071 | 0.065 | 0.115 | 0.090 |
| 9 to 11 | 1.251 | 1.380 | 1.122 | 1.223 | 1.298 | 1.060 | 0.258 | 0.238 | 0.248 |
| 11 to 13 | 1.308 | 1.358 | 1.245 | 1.326 | 1.413 | 1.263 | 0.113 | 0.150 | 0.131 |
| 13 to 15 | 1.412 | 1.454 | 1.360 | 1.440 | 1.500 | 1.339 | 0.094 | 0.161 | 0.127 |
| 17 to 18 | 1.591 | 1.658 | 1.505 | 1.537 | 1.663 | 1.432 | 0.315 | 0.281 | 0.298 |

[a]This table is a historic landmark; it is the first longitudinal growth study of a large number of infants and children from birth to the eighteenth year of life.

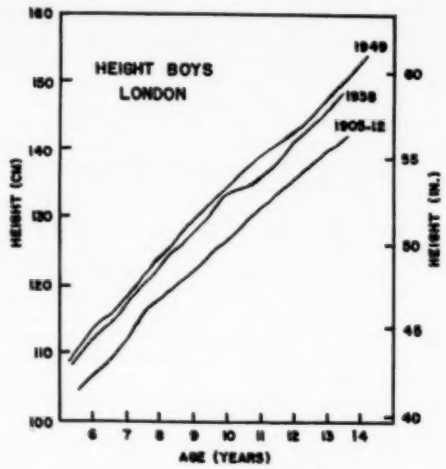



Fig. 3. Increase in stature of London schoolboys measured over a period of 45 years.

formation concerning proper health habits must all play a role. However, the actual cause is not certain; if it be nutritional, it must be some dietary change considerably more subtle than simple increase in calories. Furthermore, there is evidence that the accelerative trend antedated the era of scientific medicine[18]; Mills[19] postulates that the gradual change in world temperature conditions is an important factor in this trend.

## SECULAR TREND OF AGE OF MENARCHE

If the acceleration of statural size appears surprising, the hastening of biologic maturation, with the use of the age of menarche as an index, is even more so.

Fig. 5. Secular trend in age at menarche, 1830 to 1960. Values are plotted at year in which the average menarche took place, i.e., in "recollected-age" data if average menarche of 40-year-old persons interrogated in 1900 was 15 years, this is plotted at 1875. This places old data on the same age scale as modern probit data. When the age of interrogation was not recorded an estimated amount has been subtracted according to the nature of the population studied (primiparas, etc.). Grouping errors have been corrected where necessary (i.e., "13-year-olds" centered at 13.5 years, not 13, as in some of the older literature). (From Tanner, J. M.: Growth at Adolescence, ed. 2, Oxford, 1961, Blackwell Scientific Publications.)

Tanner,[20] more than any other current writer, has stressed the continuous trend over the last 100 years toward the earlier occurrence of puberty in children. This trend is dramatically shown in Fig. 5, which shows the changes in the average ages at menarche from 1840 to 1960 in a number of countries. During this period, it would appear that the age at menarche has been decreasing by about 4 months per decade. Tanner has also remarked that there does not appear to be any evidence that the earlier onset of menarche is decelerating. This change which is universally observed in many countries and races may be regarded as only one phase of the general world-wide quickening in the physical development of man.

A commonly held misconception is that girls in the tropics menstruate at an earlier age than those in the temperate zones. Recently, Israel[21] has shown that Indian girls have their menarche later than girls in

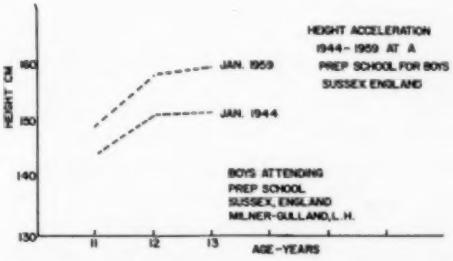
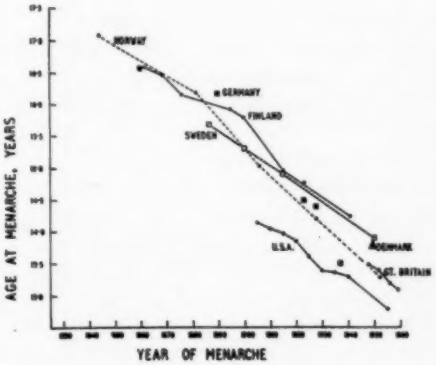



Fig. 4. Increase in stature of English prep school boys between 11 and 13 years of age during a recent 15-year period, 1944 to 1959.



England or the United States. Ellis[22] in 1950 found that the mean age at menarche of Nigerian girls was 14.2 years, while that of British nurses was almost a year earlier. May these differences be caused by such independent factors as diet, socioeconomic level, and environmental conditions? Although most investigators would consider the above-mentioned items as putative influences, the precise cause is still enigmatic.

As a corollary to this trend, should one not take this speed-up of growth into account when dealing with the adolescent because all of us tend to consider them in terms of their chronologic rather than biologic age? If growing up has been hastened, perhaps some of the difficulties encountered by parents, teachers, and even physicians, in dealing with adolescents may result from the failure to appreciate that their earlier biologic maturation may cause them to develop emotional, social and heterosexual interests at an earlier chronologic age than did their parents and grandparents. And, finally, should not this secular trend be taken into consideration as yet another but important variable in future longitudinal growth studies?

## SUMMARY

Children, at least in the United States and in Western Europe, have been growing taller and have been reaching biologic maturity at an earlier age as evidenced by available growth data for the past 100 years.

This secular accelerative trend shows no sign of slackening. Possible causes for this acceleration of growth are briefly discussed; no single factor seems responsible.

Finally, this secular trend would appear to be yet another but important biologic variable in planning future growth studies.

## REFERENCES

1. Clements, E. M. B.: Changes in Mean Stature and Weight of British Children Over the Past Seventy Years, Brit. M. J. **2:** 897, 1953.
2. Weir, J. B. de V.: The Assessment of the Growth of School Children With Special Reference to Secular Changes, Brit. J. Nutrition **6:** 19, 1952.
3. Meredith, H. V., and Meredith, E. M.: The Body Size and Form of Present-Day White Elementary School Children Residing in West-Central Oregon, Child Development **24:** 83, 1953.
4. Vogt, D.: Ueber den gegenwärtigen Stand der Akzeleration in Bayern, Arch. Kinderh. **159:** 142, 1959.
5. Wallau, F.: Ueber die Akzeleration der Menarche, Zentralbl. f. d. ges. Gynaek. u. Geburtsh. **74:** 615, 1952.
6. Tanner, J. M.: Growth at Adolescence, Springfield, Ill., 1955, Charles C Thomas, Publisher, p. 88.
7. Boas, F.: Observations on the Growth of Children, Science **72:** 44, 1930.
8. Roberts, C.: The Physical Requirements of Factory Children, J. Statist. Soc. **39:** 681, 1876.
9. Kiil, V.: Stature and Growth of Norwegian Men during the Past 200 Years, Skr. norske Vidensk. Akad. No. 6, 175 pp., 1939.
10. Cone, T. E., Jr.: De Pondere Infantum Recens Natorum: The History of Weighing Newborn Infants (to be published).
11. Quetelet, L. A. J.: Sur l'Homme et le Développment des Ses Facultés, ou Essai de Physique Sociale, Brussels, 1835.
12. Scammon, R. E.: The First Seriatim Study of Human Growth, Am. J. Phys. Anthropol. **10:** 329, 1927.
13. Bowditch, H. P.: Eighth Annual Report, State Board of Health, Mass., 1877.
14. British Association for the Advancement of Science: Report of the Anthropometric committee, 1879, London, 1880.
15. Reed, R. B., and Stuart, H. C.: Patterns of Growth in Height and Weight From Birth to Eighteen Years of Age, Pediatrics **24:** 904, 1959.
16. Milner-Gulland, L. H.: Letter, Lancet **1:** 891, 1959.
17. Stewart, T. D.: Anthropology and the Melting Pot, Smithsonian Inst., Ann. Rep. 1946, p. 315.
18. Gray, H.: Increase in Stature of American Boys in the Last Fifty Years, J. A. M. A. **88:** 908, 1927.
19. Mills, C. A.: Temperature Influence Over Human Growth and Development, Human Biol. **22:** 71, 1950.
20. Tanner, J. M.: The Development of the Female Reproductive System During Adolescence, Clin. Obstet. Gynec. **3:** 135, 1960.
21. Israel, S.: The Onset of Menstruation in Indian Women, J. Obst. & Gynaec. Brit. Emp. **66:** 311, 1959.
22. Ellis, R. W. B.: Age of Puberty in the Tropics, Brit. M. J. **1:** 85, 1950.

# *Nutritional aspects of adolescence*

**J. A. Johnston, M.D.**

DETROIT, MICH.

THE nutritional requirements of adolescence are a function of a pattern of growth peculiar to this period. A phase of accelerated speed of growth occupies about 2 years during which the evidences of sexual maturation are becoming evident; this merges into a decelerative phase terminating in a cessation of growth about 3½ years after the so-called MG year, or "year of maximum growth." A number of things are implicit in these alterations in speed. The rate of oxidation increases, in our observations,[1] in the accelerative and decreases in the decelerative phase. This carries with it a rise and fall in the calorie requirement. The ability to retain items entering into tissue structure rises and falls with the sigmoid curve of growth. In the case of nitrogen this means that marginal intakes carry with them the danger of negative balances in the decelerative phase; while the heightened capacity for retention makes this unlikely in the phase of acceleration.

There can be anticipated a normal variation of 5 years in the time of occurrence of these events, so that the clinician must think now in terms of physiologic rather than chronologic age at this time. In the boy, the adolescent pattern of growth can be anticipated to occur approximately 2 years later than in the girl. Hence the landmarks provided by the orderly appearance of secondary sex characteristics will be more meaningful than chronologic age.

Using as criteria, satisfaction of appetite, gain in height and weight, a normal basal metabolism, and a postive nitrogen balance, we concluded that the protein requirement for this group was satisfied when 15 per cent of the calories of an adequate caloric intake was derived from protein.[2] Figures lower than this and based on dietary surveys are recorded elsewhere. The calorie requirement can be predicted roughly by adding 90 per cent to the basal metabolism rate predicted from the Wetzel Grid. In the boy this is closer to 110 per cent.

We found the calcium requirement satisfied by approximately 1,300 mg.[3] This is the amount found in approximately a quart of milk. From sources other than milk, an adolescent's diet derives about 400 mg. of calcium. There is a need for added vitamin D in this climate that would seem to be greater than at other periods of growth because of the changing rates. Our studies showed that with 1,000 units, daily, the retention of calcium was greater than with smaller amounts, though there are workers who feel that it is not necessary to exceed 400 units.

## TUBERCULOSIS IN ADOLESCENCE

The abrupt increase in the incidence of the adult or reinfection type of tuberculosis

*From the Henry Ford Hospital, Detroit, Mich.*

in the adolescent has long been associated in the physician's mind with some change which lowered resistance at this time. We were able to demonstrate a direct relationship between healing and the adequacy of nitrogen storage in those children in whom the disease developed. We showed also the diminished retention incidental to the decelerated growth that followed the menarche in girls.[4] The inference from these 2 studies was that there was a causal relationship between the diminished capacity to retain nitrogen and the occurrence of endogenous reinfection. There was implied the necessity for actually prescribing the protein intake at this age, particularly for the tuberculin reactor.

## OBESITY IN ADOLESCENCE

In the middle and upper economic strata in this country this is a far greater problem than undernutrition. The role of psychogenic factors and the exclusion of thyroid deficiency in its causation have been stressed by Bruch.[5] It would be an oversimplification, however, to dismiss the problem as psychogenic overeating. The facts have been verified that they may actually eat less than their thin companions but be far less active,[6] and we have long underestimated the role of exercise. An actual pathologic lesion involving the hypothalamus or the anterior pituitary has been postulated and constitutes an objective for rewarding study. Meantime, our only approach will involve diet, exercise, and sympathetic handling of the psychogenic difficulties that in our thinking are as frequently a result as they are a cause of the difficulty. In prescribing a diet in which calories are reduced, the protein should be increased. In particular we stress a high protein breakfast for the added protection against the low blood sugar that is often a source of hunger later in the day.

## EPIPHYSIOLYSIS

Slipping of the upper femoral epiphysis is a disturbance almost limited to the year of maximum growth during adolescence, on the average the twelfth in the girl and the fourteenth in the boy. While the theory which regards this as an evidence of a relative excess of growth over sex hormone production is probably the most tenable, the fact remains that the poor or absent calcium retentions that we demonstrated in patients with this disturbance could be improved with an adequate intake of calcium and vitamin D.[7] Since there has also been shown to be a reciprocal relationship between gain in weight and calcification of bone, it is our feeling that the pediatrician has a real contribution to make in the prevention of this disorder. In the preadolescent who is overweight, the risk of this lesion should be pointed out and the plan to limit weight gain set in motion well before the occurrence of the adolescent spurt when it is so difficult to control. The need for vitamin D in this group seems not generally appreciated.

## REFERENCES

1. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in the Growth Period. III. Puberty in the Normal Girl and in the Girl With Minimal Reinfection Tuberculosis, Am. J. Dis. Child. **59:** 287, 1940.
2. Johnston, J. A., and Maroney, J. W.: A Study of the Caloric and Protein Requirement and the Basal Metabolism of Children From Four to Fourteen Years, Am. J. Dis. Child. **54:** 29, 1937.
3. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth, Am. J. Dis. Child. **67:** 265, 1944.
4. Johnston, J. A.: Nutritional Studies in Adolescent Girls and Their Relation to Tuberculosis, Springfield, Ill., 1953, Charles C Thomas, Publisher.
5. Bruch, H.: Psychiatric Aspects of Obesity in Children, Am. J. Psychiat. **99:** 752, 1943.
6. Heald, F.: Obesity in the Adolescent, Pediat. Clin. North America **7:** 206, 1960.
7. Johnston, J. A., Manson, G., and Mitchell, C. L.: Epiphysiolysis, A. M. A. Am. J. Dis. Child. **92:** 337, 1956.

# Variations in personality growth during adolescence

**Richard E. Wolf, M.D.***

CINCINNATI, OHIO

ADOLESCENCE may be defined as that period in the life of a person when the society in which he functions ceases to regard him as a child and yet does not accord him full adult status, roles, and functions. Thus, we see adolescence not as a chronologic period, but rather as a physiologic, psychological, and sociologic span.

Though we know that special physiologic changes begin to occur from age 10 to 18, these are only some of the changes and reaction to change which characterize the adolescent. The setting in which the adolescent changes are taking place is important to understand. The adolescent must attend school until he is 16 (in many instances he continues to be a student well into his twenties). He is not permitted a full-time job until 16. At age 18 he is subject to the draft, but he does not acquire full citizenship rights until he is 21. All of this is without regard for the rate of his own physiologic and psychologic maturation. Just as there is variation in physiologic development during adolescence, there is also tremendous variation in personality development. This is complicated by the fact that growth is occurring during a period when internal changes are taking place and while the environment is reacting to the altered behavior brought about by these changes. Sometimes it is difficult to ascertain how much of the behavior of the adolescent results from changes within him, and how much derives from the reaction of the environment to him.

There has always been concern on the part of the adults of a culture for the adolescent, and the place of the adolescent in the culture varies with the culture. Among primitive tribes physiologic maturation and initiation ceremony entitled the adolescent to enter the adult culture without difficulty. However, in our culture, where the gap is great between physical maturation and "sociologic maturation," psychologic adjustment will be more complex. Certainly there is increasing concern for the adolescent and also concern about him. A fair portion of this concern grows out of the anxiety aroused by the pathology of adolescence. Even the term "adolescent" signifies to many adults something worrisome and, therefore, pathologic. To most people, "juvenile" has become associated with "juvenile delinquent." Although this is unfortunate, it is not hard to understand

*From The Children's Hospital, Department of Pediatrics, University of Cincinnati, College of Medicine.*
**Address, Children's Hospital, Cincinnati 29, Ohio.*

when it is realized that knowledge about adolescence comes, for the most part, from psychiatrists, social workers, and psychologists who see disturbed adolescents. The pediatrician, or family physician, who might have had the opportunity to see the healthy adolescent has not had the time or has not felt adequate to deal with him.

In this symposium an attempt is made to outline normal adolescent development and to emphasize the normal variations during this growth period. Whether one refers to physical, intellectual, social, or emotional growth, the emphasis is on the positive, healthy aspects of growth between the ages of 12 and 22. This makes adolescence "the age of the final establishment of a dominant ego identity," as Erickson puts it, and "it is then that a future within reach becomes part of the conscious life plan." To look forward to the future implies standing in the present, having traveled from the past. Whether remembered or not, the "before" cannot help but affect the "now" and the "to be."

If the adolescent would ask his own questions, they would probably be something like this:

*"Who* and *what* do *they* think I am?"

*"What* do I *feel* I am, and *what* should I *become?"*

The search for the self in relation to the group is the developmental task of this period. How does this come about? In the search for the answer to the first question, "Who do they think I am?" the adolescent is dealing with his own identity. In finding his identity he must adjust his ego to the social environment. In other words, this is concerned with ever more development *outward,* toward those functions of the ego that are apparent to others. This can be called the sociocentric function of the adolescent ego. The second question, "What do I feel I am and what should I become?" refers to the adaptation of the social environment to the ego. This involves ever more development *inward,* within the bounds of the ego, and a concern with what he feels himself to be—his role. This can be referred to as the egocentric function of the ego.

Individual variations in personality growth during adolescence make it difficult to describe adolescents as a group. Variability from adolescent to adolescent (and the changes within the same adolescent within short intervals of time) is perhaps the most characteristic feature. The variations of physical growth, the timing of environmental changes, and the accidents and events of the individual's past will help determine the pattern of the personality that unfolds during adolescence.

Besides variability, there are 2 main areas of change shared by all adolescents: the reawakening sexual interest and the pressure from within to be freed of dependence. The wish to be loved, now enhanced by biologic sexual urges and stimulated by the desire for independence, now has increased primitive strength. The pressure to be freed of dependence carries with it denial of the standards of the parents, in favor of strong acceptance of the philosophy determined by the peer group.

The degree of activity in expressing these 2 characteristics of the adolescent comes from something that can be called *sensation hunger,* which means the capacity to feel deeply and to invest tremendous energy in sensation. This voracious sensualism of the adolescent easily frightens the more mature members of his culture. He seems to have to get a kick or thrill out of something, to feel intensely, to have new experiences, new sensations. He chooses the music that will "send" him, he dramatizes self-visualization as he suffers and exults with a Castro. He invests his entire being in a school pep rally. This sensation-hunger is usually sublimated in cultural activities, sports, intellectual pursuits, in social or political activities. Witness a teen-age project at a high school or recreation center and note the elaborate production of a play with original sets and electrical work all done by the youngsters, and one sees the energy that can go into such an activity. Similarly, the elaborate planning for a party; the "before-the-party" and the "party-after-the-party" are examples of sublimation of this sensation-hunger. Sometimes

it may be expressed in "risk thrills," like driving a car too fast. The sensation of being in danger or wanting to master the anxieties involved in the threat of physical danger seems to be one of the tasks he assigns himself. His ability to sublimate is working well when he expresses this need by participating in difficult sports, like skiing, mountain climbing or skin diving.

As if this were not difficult enough, it alternates with the idealism of the adolescent. Now he seems to be holding himself to standards of behavior too rigid for comfortable living, even to the point of asceticism. By this means, the ego of the adolescent is bombarded by pressures which temporarily weaken it and results in unpredictable behavior and mood swings so marked that, in a more crystallized personality, it would be indicative of serious disturbance.

The situation brought about by his own stage of physiologic maturation, the environment in which he finds himself, and the key persons involved, is not all the adolescent must deal with. Problems of his past adjustments are unharnessed again. But now he has another chance to solve these problems that were incompletely solved in an earlier period of childhood. With the new skills and aptitudes that come from a larger, stronger, and a changed body apparatus, any residue of feelings of physical inferiority can be dissolved and increased feelings of self-worth liberated.

Perhaps nothing so characterizes the struggle of the adolescent as the conflict with his parents. There is a rather pathetic inevitability about this; the adolescent is what he is because of the relationships he has had with his parents and the sort of experiences he has had. There has been love and there has been identification and his conscience has had its origins in that of parents. Dependency upon another person can be an indication of maturity or immaturity. When the adolescent tries to deal with his world as he did in childhood, he finds it quite different. The increased responsiveness to his environment that he feels and the internal needs accompanying his physiologic changes create for him new and baffling situations. The drive for more independence gets in the way of asking advice, so he blunders into situations that he finds difficult to handle. If he becomes frightened and turns to parents or other adults for support, he dare not permit himself the reassurance he needs, and could get, from a mature dependency relationship. Instead, he may regress and return to the old familiar pattern of infantile dependency. But if he does this, he sees himself as having returned to childhood and to him this means abandoning his struggle to become adult. This is such an intolerable blow to his pride that he resents the dependency for it has threatened his confidence in himself. In order to protest against his own weakness (which he wishes to deny) he protests angrily that his parents will not let him grow up and that they treat him like a child. Temporarily, it may seem easier to be angry at parents than to accept his own weakness.

However, he wishes to grow up. In wishing this, he needs to tear away the roots of his conscience from the parent figure and to be able to trust in himself. And then the parent, having given some permission for him to grow up and modify the character of his social life, etc., is frightened by the apparent instability of the adolescent, tending to inhibit him where freedom was formerly implied. Now the choice of his friends may be the ones that seem calculated to be unacceptable to his parents. Often these are new friends or old acquaintances from former days, now drawn together by mutual interests, compatibility of tastes, and shared annoyances with the adults about them. While he protests his adequacy to care for himself, he shows how frightened he is to do this, frightened by his own impulse to emancipate himself. Actually, when his quandary becomes severe, the adolescent regresses, asking for more limits, for decisions to be made by the parents, etc. In this paradox, perhaps, lies the explanation of why it is that, no matter how wise a parent may be, he can never be right for any length of time with his adolescent child. To under-

stand and accept the desires of the adolescent and at the same time be able to relinquish parental controls and transfer responsibility to him requires a neat measure of adjustment and security on the part of the adult.

When the standards of the particular family and the standards of the community in which they live are quite similar, there is less adjustment difficulty for the young person than there is when there is a wide discrepancy between the standards of his family and those of the community. Here it is that the difference between the philosophy of the peer group may pull strongly in one direction and the pull of the identification and loyalty to parents in another. When the difference is great, various defensive reactions become possible. Well known is the submission versus rebellion reaction, or the development of a psychosomatic illness to keep the adolescent incapacitated and free from decision-making. Often, fortunately, the adolescent and his parent can interact in a situation where each recognizes his *disagreement* but neither considers it indicative of *disturbance* in the other.

An analogy can be drawn between the development of America, as a nation, and the development of each American adolescent. Just as America is a melting pot made up of people from different backgrounds, so is the adolescent personality made up of identifications from multiple sources in his background. An American today grows out of what he has come from, been exposed to, and wants to become. An adolescent is what he is, based on what he has come from, his parents, and what he has been exposed to, to which he adds his ideas of what he is to become. Just as America tries to establish for herself a superidentity from all the identities of her constituent immigrants, and thus find a dominant identity, so too does the adolescent need to be able to sink his roots in established tradition and institutions, but still have within him the frontiersman's urge to venture beyond, to find the new, the unestablished, and thereby push the culture a little further. Piaget said "the adolescent is committed to possibilities." The hope for him is that he has good ones from which to choose, that he has the self-assertion to create something new, and that the adults, his parents, are willing for him to have greater success than they.

## REFERENCE

1. Erickson, Erik H.: Childhood and Society, New York, 1950, W. W. Norton & Co., Inc.

# The zone between social acceptance and juvenile delinquency

**Thomas E. Shaffer, M.D.***

COLUMBUS, OHIO

DELINQUENCY is not a new term or a new phenomenon. Frequent use of the phrase "juvenile delinquency," and extensive publicity about it have brought to the situation in recent years a notoriety which would be impressive even if there were no increase in occurrence. There are good reasons for all citizens, and especially for children's physicians, to be interested in antisocial behavior of children, for it is an acknowledged problem of the day and appears to be more conspicuous as the years pass.

The number of juvenile delinquency court cases tripled between 1940 and 1958 which is a far greater increase than that in child population in the same period. In any year a little more than 2 per cent of all children aged 10 through 17 years will be referred to juvenile courts. A better idea of the size of the problem is gained from an authoritative estimate that 12 per cent of all children will at some time during their years of 10 through 17 be referred to courts. Roughly 20 per cent of all boys will, during this age period, be referred to courts, for the ratio of male to female delinquents is 5:1.[1]

These statistics refer only to official or legal delinquency, the violation of laws or codes which leads to appearance in court. Only a small part of delinquent behavior comes to official attention. Moreover, of those who are picked up by police, only 1 of 4 reaches the court. The rest are returned home with a warning or placed in custody of the parents by the police.

In the Cambridge-Sommerville Youth Study[2] it was found that very little violational behavior came to the attention of the courts. Over a 5-year period of observation only 13 of 114 boys selected for special study were observed to be free from commission of an offense. The remaining 101 boys committed a minimum of 6,416 legal infractions in the 5 years, only 95 of which came to the attention of the court. Only 0.6 per cent of minor violations such as running away, truancy, petty stealing, and trespassing came into court. Eleven per cent (68 of 616) of serious offenses, such as breaking and entering, larceny, sex offenses, assault and drunkenness were brought into court.

Nonreporting of juveniles' violations introduces a significant factor into an understanding of statistics on the incidence and nature of juvenile delinquency. If there is bias in the reporting of juvenile offenses, statistics do not mean very much. It is undoubtedly true that there is great variation in the extent of complaining about viola-

*From the Department of Pediatrics, The Ohio State University, Columbus, Ohio.*

**Address, 2280 West Broad Street, Columbus 4, Ohio.*

tional behavior. One factor is social class distinction. It is estimated that 85 per cent of juvenile delinquency, as legally defined, occurs in the lower socioeconomic levels of society.[3] Some but not all of this disparity between lower and middle class behavior can certainly be explained by differences in reporting of children to the police. Sociologist Porterfield has said: "The court child is from a socially unimportant family" and is "friendless."[4] The unimportant person has a much greater chance of having his or his children's violations brought to official attention than the individual with influential friends.

If it is contended that juvenile delinquency does not exist until the child's case reaches court, it should be recognized that the persons, procedures, and biases responsible for bringing children into court have as much or more to do with delinquency data than does behavior of the juveniles themselves.[5] One should, therefore, be hesitant to accept statements about differences between delinquent and nondelinquent samples of the child population. Certain classes of children get reported more often than others—boys more than girls, lower class more than middle class, some minority groups more than others. This point is stressed for it has often been said that pediatricians have no chance to influence juvenile delinquency because it occurs only among children who do not have private physicians. There is more antisocial behavior among the "private-patient type" than is recognized.

Crime and delinquency in underdeveloped areas of the world are precipitated by poverty, lack of food and employment, inadequate housing, poor schools, and other deprivations. What then is the cause in the United States where living conditions are favorable, where there is plenty of food, where children go to school, and most families are not affected by unemployment?

## SOCIOLOGICAL THOUGHTS ON ETIOLOGY

As physicians, brought up on the requirement for fulfilling Koch's postulates in establishing the etiology of an infectious disease, we would like to see a single factor solidly implicated. Others outside the circle of medicine have also had this idea. Impressed by the high incidence of delinquency in the lower class, sociologists have often searched for causes in the cultural milieu. There are indeed many factors in lower class social structure which contribute to delinquency, such as association with criminals and delinquents,[6] identification with a criminal model,[7] companionship with other boys in gangs,[8] and the existence of the so-called delinquent subculture,[9] which is the milieu in which an unhappy or unstable working-class boy can express his hostile feelings about his way of life and about middle class standards. In this way the child handles questions about his status—he joins a gang of similarly disgruntled boys as his response to middle class norms, such as school, achievement, ambition, etc.[10]

This delinquent subculture, which does not necessarily exist only in lower socioeconomic levels, becomes a way of life in which youths take special satisfaction in defying taboos. Standards are "right" in the subculture if they are "wrong" by middle class norms. This theory contributes substantially to understanding of delinquency in slum areas.

Other sociologists have tried to explain delinquency on the basis of class structure alone. This aspect of the problem has been described in a report of the National Education Association's Juvenile Delinquency Project. It was pointed out that there are dominant concerns in lower class culture: *trouble* (a concept of generalized difficulties), *toughness,* (physical strength, masculinity), *smartness* (skill at tricking the other fellow), *excitement* (thrill and stimulation), *fate* (philosophy that good or bad luck is a predominant factor in life), and *autonomy* (resistance to being bossed or controlled). These qualities lead to "normal" behavior which violates standards set up by middle class society in which the norms are based on a different set of values: achievement by work, deferment of immediate gains for fu-

ture goals, maintenance of family unity, accumulation of material goods, maintenance of property, and ambition to get ahead.[11] Thus, it is held that children in lower class culture are delinquent out of proportion to their misdeeds because they engage in certain cultural practices like playing hookey, destroying property, taking small objects, and having gang fights, which are essential conduct in their culture but automatically violate certain legal norms, predominantly established in this country by middle class society.

Logical and true as these sociologic explanations may be, the fact remains that, in spite of their particular environment and cultural norms, most lower class youngsters do not come to the attention of law enforcement agencies. There must be more to the causes of delinquency than lower class living and street corner society. It has been said that the aspirations of lower class children to move upward socially, in a real acceptance of middle class standards, determines the nondelinquent behavior of most lower class children. Some sociologists, too, believe that norm-violating behavior of middle class youngsters may become more prevalent in the future as the result of borrowing of some lower class concerns by the middle class.

If, as has been mentioned, delinquent behavior requires a push from within the youngster related to his needs and an environmental milieu for expression of his needs, a look at the child's own personality structure in relation to delinquency is pertinent.

## NEO-FREUDIAN THOUGHTS ON ETIOLOGY

Psychoanalysts have been much concerned with juvenile delinquency and have offered many explanations. Perhaps the most outstanding applications of Freudian theory to the problem have been those of Aichhorn, Friedlander, and Redl. Aichhorn[12] states that the delinquent child is an "asocial being," almost exclusively interested in direct instinctual gratification. If his early upbringing is faulty, these drives will only be suppressed, ready to break through for gratification at a timely opportunity. He believes that delinquency is more than antisocial behavior, having characteristics of a neurotic symptom, but lacking the qualities of discomfort and unpleasantness typical of neurotic symptoms. He feels that delinquents have little capacity for repressing instinctual impulses or for directing their energy in controlled channels. His concept is in some ways allied to the concept of lower class concerns mentioned earlier when he compares the delinquent to "the child who is not able to give up immediate pleasure for later satisfactions," except that he attributes this characteristic to faulty ego development predisposing to delinquent behavior: excess of love (especially as overgratification by the mother), excess of severity (usually an authoritarian or overrestrictive father), and an alteration between the oversolicitousness of the mother and the punitiveness of the father.

Fritz Redl,[13] an Aichhorn disciple, has made significant contributions to the understanding of aggressive, hostile children. Children who hate, according to him, have a "delinquent ego" which permits the child to have guilt-free and anxiety-free enjoyment of delinquent, impulsive behavior.

While these psychogenic explanations undoubtedly contribute to understanding of many cases of delinquent behavior, the fact is that the majority of juvenile offenders are not emotionally disturbed. According to one estimate the preponderant proportion (75 per cent) of the delinquent population are normal youngsters. There is some disparity in the distribution of emotional disturbance among upper and middle class delinquents (twice as many emotionally disturbed as showing no symptoms) compared with lower class offenders (1 emotionally disturbed to 4 not so affected), but this is probably more apparent than real, because more offenses not due to psychogenic causes are reported among lower class children.[14] The offenses which cannot be accepted in middle class society and are invariably brought to court

(arson, homosexuality, molesting, shop-lifting, and homicide) occur predominantly in emotionally upset children. Therefore, the psychogenic explanations of delinquency do not account for most of the cases.

Although there is some effect on children's behavior from peer group associations, churches, schools, and individual acquaintances, the family exerts the most important control over adolescents' behavior. In the lower class social structure, particularly, the family is notoriously unstable, loose-knit, and different in that it is often female-centered with an absence of a stable father figure. There are variations in the quality of family life in the middle and upper classes as well. It is not necessary to suppose that the extremes of faulty personality development in the early years of life, exemplified by emotional disturbance or "sick" children, are the only explanation for antisocial behavior. Where there are inadequate supervision of the child at home, lack of warmth and affection, no reasonable and consistent limits on aggressive behavior, lack of a father, overgratification, or severe punitiveness, separately or in combination, socially acceptable behavior cannot develop.

## PREDICTION ON BASIS OF FAMILY ITEMS

Recognizing the influence of family climate on children's personality, Sheldon and Eleanor Glueck[15] have used 5 aspects of family relationships to design a prediction scale by which to prognosticate, early in life, a child's chances of future delinquency. The factors, weighted and scored in a prescribed way, are:

1. Discipline of the boy by the father (overstrict; erratic; lax; firm but kindly).
2. Supervision by mother (unsuitable or suitable).
3. Affection of father for the boy (indifferent; hostile; warm).
4. Affection of mother for the boy (indifferent; hostile; warm).
5. Cohesiveness of family (unintegrated; some cohesion; cohesive).

This prediction scale has been given thorough trial in New York City among children ranging from 5 to 6½ years of age and has been found to be significantly effective.[16] The import of such a scale, even for physicians who are in position to evaluate family relationships, is obvious.

Another method for predicting delinquency during the early years of a child's life, which physicians could use to complement critical evaluation of the family as suggested by the Gluecks, could be based on serious attention to parents' complaints about their children's behavior. Careful analysis of the early life of juvenile delinquents reveals that parents have been troubled by these children's disobedience, lying, and running away during the 4 to 6-year age period. Such behavior is significant and potentially a precursor of delinquency in the right family and community setting.

W. C. Reckless,[17] a sociologist, has pointed out that there is no *single* cause of delinquency in the United States. All of the factors discussed may in certain instances operate alone or in combinations. In attempting to explain the increasing amount of delinquency, he introduces the concept that in our society today there is a "lack of containment," a lack of well-defined limits to behavior, and an absence of definite roles for adolescents to play. He says, "It is as if adolescent life were played without script, without definite parts and directions." Automation in industry and our fluid society in which communication and travel are unimpeded have affected the inner and outer controls.

Reckless and Dinitz[18, 19] have shown that one of the insulators against delinquency in early adolescence is a good concept of self, family, school, and associates. Poor family relationships, failure to find a role in society, and concerns about status contribute to poor self-concept.

If prediction methods and case-spotting by teachers and others can reveal vulnerable children, it should be possible to instill more inner controls into normal children and to build up more containment in the environment.

## MEDICAL CONCERN

Deisher's[20] investigation of the early medical background of more than 100 juvenile delinquents showed that the parents of these children had been concerned about them for many years and they had consulted physicians years before, in most cases as the first search for help. Deisher concluded that parents of potentially delinquent children do not receive the help they need, except in the few instances when the problem is a physical one.

The pure and simple medical aspect of juvenile delinquency is almost nonexistent. However, because physicians are in the strategic position of being family counsellors for parents of young children, regardless of whether the problem is physical or behavioral, it follows that physicians in their practice or in community clinics are offered a most influential role in recognizing and controlling delinquent behavior.

The physician's role in delinquency would appear to be a real one, based principally on early recognition of symptoms of antisocial behavior and wider understanding of the causes contributing to its development. His responsibility does not end merely with recognizing and defining the problem, but extends further to active interest in and support of nonmedical community programs, where the real progress in delinquency control will be found.

## REFERENCES


1. Perlman, I. R.: Delinquency Prevention: The Size of the Problem, Ann. Am. Acad. Polit. & Social Sc. **322:** 1, 1959.
2. Murphy, F. J.: Delinquency Off the Record, National Probation Association Year Book, New York, 1946, pp. 182-183.
3. Kvaraceus, W. C., and Miller, W. B.: Delinquent Behavior: Culture and the Individual, Washington, D. C., 1959, National Education Association, pp. 55-56.
4. Porterfield, A. L., and Clifton, C. S.: Youth in Trouble, Fort Worth, 1946, Leo Potishman Foundation, p. 48.
5. Reckless, W. C.: The Crime Problem, ed. 3, New York, 1961, Appleton-Century-Croft, Inc., p. 370.
6. Sutherland, E. H.: Principles of Criminology, ed. 4, Philadelphia, 1947, J. B. Lippincott Co., pp. 6-7.
7. Glaser, D.: Criminality Theories and Behavioral Images, Am. J. Sociology **61:** 440, 1956.
8. Eynon, T. G.: Factors Related to Onset of Delinquency, Columbus, 1959, Ohio State University Ph.D. Dissertation, pp. 17, 36.
9. Cohen, A. K.: Delinquent Boys: The Culture of the Gang, Glencoe, Ill., 1955, Free Press, pp. 50, 59, 65, 70.
10. Cohen, A. K.: Delinquent Boys: The Culture of the Gang, Glencoe, Ill., 1955, Free Press, p. 30.
11. Kvaraceus, W. C., and Miller, W. B.: Delinquent behavior: Culture and the Individual, Washington, D. C., 1959, National Education Association, pp. 64-67.
12. Aichhorn, A.: Wayward Youth, New York, 1936, Viking Press, pp. 200-203.
13. Redl, F., and Wineman, D.: Children Who Hate, Glencoe, Ill., 1951, Free Press, pp. 142-144.
14. Kvaraceus, W. C., et al.: Delinquent Behavior: Culture and the Individual, Washington, D. C., 1959, National Education Association, p. 63.
15. Glueck, S., and Glueck, E.: Unraveling Juvenile Delinquency, Cambridge, 1950, Harvard University Press, p. 261.
16. Whelan, R. W.: Environmental Causes of Delinquency, in F. J. Cohen, editor: Youth and Crime, New York, 1957, International Universities Press, Inc., pp. 65-66.
17. Reckless, W. C.: The Crime Problem, ed. 3, New York, 1961, Appleton-Century-Croft, Inc., pp. 335-359.
18. Reckless, W. C., Dinitz, S., et al.: Self-Concept as an Insulation Against Delinquency, Am. Sociol. Review **21:** 745, 1956.
19. Reckless, W. C., Dinitz, S., et al.: The Self Component in Potential Delinquency and Potential Non-Delinquency, Am. Sociol. Review **22:** 769, 1957.
20. Deisher, R. W., and O'Leary, J. F.: Early Medical Care of Delinquent Children, Pediatrics **25:** 329, 1960.

# *The doctor and other factors in adolescents' health and illnesses*

**J. Roswell Gallagher, M.D.***

BOSTON, MASS.

TODAY we have been asked to consider the effects which the environment, and particularly the doctor, can have on an adolescent's health. A large order, but, because we have met to honor the memory of Graeme Mitchell, it is an especially appropriate topic for us. Of the major environmental factors affecting adolescents, people stand first. Dr. Mitchell had in abundance those qualities—warmth, kindliness, empathy, good humor—which serve adolescents well. He liked them. These qualities and how you feel about young people can benefit them as much as what you know about them.

Before we review the ways in which cultural factors, parents, companions, doctors, and other people affect young people's development, it may be well briefly to remind ourselves of what adolescents are like. Were we talking about younger or about older people whose characteristics and needs differ from theirs, the effects of these factors would not be the same.

*From the Department of Pediatrics, Harvard Medical School, and the Adolescent Unit, Children's Hospital Medical Center, Boston, Mass.*

*This study was aided by a grant from The Grant Foundation, Incorporated.*

**Address, Chief, The Adolescent Unit, Children's Hospital Medical Center, Boston 15, Mass.*

Among the adolescent's outstanding characteristics are the rapidity of growth and the capacity to change. He is the opposite of all that is static or accurately predictable. The rapid growth in linear height brings awkwardness, self-consciousness, and the sort of posture adults sometimes object to; it brings unique nutritional demands and the need to give special thought to such matters as stressful sports, scoliosis, and fractures through epiphyses.

There are rapid changes in many areas: in the sebaceous glands, bringing acne; in the sweat glands, bringing offensive odor and further adding to the adolescent's stockpile of self-consciousness; in higher levels of androgens and estrogens, bringing the menarche, bodily changes, and new drives and new thoughts; in increased resistance to infection, permitting a relaxation in restrictions; and in other tissue growth such as that of heart size and blood volume, which require consideration when evaluating the child with a damaged heart.

There are psychological changes too. Adolescents are resilient; variable in mood and behavior and interests. They often improve and decline in an unexpected fashion, so they demand flexibility in those who would deal with them, and make long-range predictions and long-range prescriptions hazard-

ous and inappropriate. Those traits, and the greater concern with sex, the changing feelings toward each parent into those more appropriate to an adult, the acquiring greater ability to be independent, the concern about school, and the developing of an adult conscience, their own points of view, and knowledge of where they are going—each of these we need to take into account when thinking about them. Each, though at times painful for the adolescent and annoying to the adult, is normal and natural. We may be upset by their acne or by their awkward strivings to be independent, but the underlying processes—the rise in androgen levels from childhood toward adult ones and the shift from a state of dependency toward independence—are as desirable as they are inevitable. Furthermore they can, and often do, proceed smoothly and without causing disease or conflict. Adolescence is not always a period of excessive stress and discord.

True as that is, the physical and physiologic processes which go on at this time of life too frequently furnish young people with one or another problem which they and we would like to prevent or to manage more effectively. What can we doctors do? How can we, as part of their environment, be of most benefit?

Though we should not forget those genetic factors which make every individual unique and which should be taken into account in our thinking about each patient, it is more profitable here to consider that the answer to these questions and to the question, "What can we do about adolescents?" lie primarily in a consideration of what we can do about little children. It is the very early years which count most. If they are good ones, the chances that adolescence will go smoothly are significantly increased.

At birth it is not too soon to think of preventing the normal processes of adolescence from creating problems. This is the time to begin to help young people and to help their parents. Later it will do little good to answer the worried parents' question "What did I do wrong?" If in the first year parents intuitively or through their doctor's or other's counseling see to it that the baby's needs are gratified; that in the next 2 years he can express warm feelings, develop spontaneity, and learn that there are limits; that in the years before he goes off to school he can experience a feeling of integrity in his family and from this learn, by good example, those interpersonal relationships which are the basis for a good sexual adjustment—then there is less likelihood that in adolescence he will be resentful, demanding, suspicious, unable to accept authority, overly anxious about sex or about becoming an adult, or need to seek recognition in socially inappropriate ways.

Soon many other people and many factors outside the home begin to exert their influence on the child. When their own households are small, with few cousins, aunts, uncles, grandparents, and brothers and sisters about—and, therefore, less opportunity to get to know both sexes, fewer people to depend upon and to learn to defer to, and a greater chance that ties to parents may become so strong that later they will not easily loosen—under those conditions the adjustment in adolescence may be more difficult. In this modern world this factor frequently obtains: some parents will need and welcome our suggestions of ways to counteract it.

Though the years from 6 to 12 are sometimes (and from some points of view not fortuitously) called "the latency years," their great importance to the future adolescent may need interpretation to parents and teachers. If they are joyful, friendly, successful years, the child will bring to adolescence a feeling of confidence in himself and a feeling of competency which he so badly needs if he is successfully to meet his new challenges. Erikson has warned, "The danger in this period is the development of a sense of inadequacy and inferiority in the child who does not receive recognition for his efforts." This is when a lack of scholastic ability takes its toll, especially when no compensatory athletic, social, or artistic talent exists. It is a time when an unhappy, sarcastic teacher; a parent who can never give unqualified praise; or a bully contemporary can warp

attitudes and feelings. These are the years when excessive fat, very frequent illness, protruding ears, severe malocclusion or myopia, or other physical handicaps which interfere with success and acceptance need more than casual attention. Not only the conditions themselves, but their effect on the boy's or the girl's preparation for adolescence, need consideration.

A good start in the early years is always to be hoped for, but it is not all. Even with the best of starts, subsequent unfavorable factors can make adolescence difficult, but fortunately adolescents are resilient. Since at this time they again re-live their early conflicts, and since they have not yet developed strong defenses nor deeply repressed their worries, even with a poor start much can still be done to help them help themselves over these years.

Adolescents would seem likely to do best in a society which is not so highly competitive that they always feel pushed and always feel hurried to make up their minds, to form their plans, to develop their attitudes, to change their feelings. You no doubt have heard them complain, "If I just sit, and perhaps dream for a minute, they want to know what I'm doing, why I'm not studying, why don't I invite Susie to the dance." He feels he has little time to think, to let his ideas catch up with his body; his idealism is in conflict with the materialism all about him; he doesn't know where he's going and he'd rather not start; he feels forced to take his ideas at second-hand or to be trampled on, so he may give in, or become anxious, or do a beatnik or other sort of retreat. In a world or in a home characterized not only by competitiveness but also where so many choices are offered, young people's confusion is compounded. Yet the choices—of religion, of careers, of places to live, of standards of conduct, of beliefs—must be made, and must be made at a time when the child's confidence in himself is low, when his former heroes and beliefs may be falling, and when he is attempting to re-adjust his feelings toward his parents and to develop independence.

Some of this, the competitiveness of our society and the multitude of present-day choices which our ever-smaller world presents to our young people, cannot be changed even if we would. We can, however, do much to help these young people meet these conditions. Young people need an adult's interest, support, guidance, respect, and praise, but only to the extent that these foster their confidence and their independence, not to the extent that these keep them dependent or increase their insecurity. Unsolicited advice, constant suggestions, and prodding and helping, criticism but never praise without a qualifying "but" ("That's good—it's better than you've ever done before, but next time do better"), meeting each idea of theirs with a better one, clinging to them in a possessive way—these are hardly calculated to increase confidence, independence, and initiative or to make it easier for these young people to meet their present challenges and to become responsible, mature, effective adults.

Just as in the child's earlier years the doctor has 2 roles during the years of adolescence, explaining the needs of the child to parents and in so treating disorders that they interfere as little as possible with the child's gaining competency and acceptance. The doctor's first role is to interpret to parents their son's or daughter's new needs, to advise and to help them in meeting these, and to allay the parent's own anxieties. Since adolescents are changing, so too should parents change their feelings, ways, and objectives. They should yield possession, think of helping to make a man, not just of bringing up a child. For those parents who are insecure and anxious themselves, it is not an easy time.

The doctor's second role is in so caring for adolescents' disorders that their changing physiology, their overconcern with their bodies, their changing feelings toward sex, their need for those activities which yield them recognition and confidence, and those genetic factors which make each individual different in greater or lesser degree from all others, are all taken into account. By so doing he becomes an ally in their environ-

ment; when he doesn't, he may unwittingly let their bodies and their disorders work against the adolescent's staisfactory development. Their growth as in height, breast development, and sexual maturation, their acne, their obesity—these are matters whose effect upon their adjustment concern the doctor as much as they worry boys and girls, and in great part for the same reasons. Knowing their concern with their bodies and their heightened and changing sexual feelings he tries to arrange such surgical procedures as orchidopexy or cardiac surgery when they are needed before puberty; he takes gynecomastia into account; he drapes the child during examination, and he avoids the vaginal examination of the young adolescent girl; and if a brace is needed for scoliosis, he gives thought to its cosmetic effect. Recognizing that hereditary factors make for differences in rate and pattern of growth, in biochemical pattern, in response to therapeutic measures he avoids the concept of the average and thinks instead of individual differences. Realizing the need for the confidence which success in activities can yield, he avoids restrictions whenever he can; when he cannot, he tries to substitute other sources of recognition. He strengthens rather than protects or rests so that activity and stress will be less likely again to produce injury or fatigue. He remembers the worries such matters as marriage and a job bring to those who have a chronic or handicapping disorder, the nutritional needs and personality problems of those who are obese, the special reasons for this age group's menstrual complaints, and the common causes of their psychosomatic problems and anxieties.

Finally the doctor, as a factor in the adolescent's environment, has a third role. It is not a role for him alone; he may share it, play it alone, or leave it all to a teacher, a coach, an employer, a member of the clergy—any adult whom the adolescent likes and respects. Whoever this may be, not infrequently and surely in time of stress, as adolescents break away from home, they will feel the need of support. Not yet able to stand alone, but hesitant in this time of breaking away to turn to those to whom they are so closely tied, they may seek the temporary support of, and need to talk with feeling and confidentially to, some adult outside their family. Given the opportunity to see him alone, and to sense his interest and respect, this important function can be their doctor's.

The environment clearly is not all, and of the long list of people who affect the adolescent, the doctor is but one. However, the doctor who thoughtfully counsels children's parents and teachers in the early years, who changes his thinking about young people to fit their changing bodies and emotions, as they grow up, and who will always be ready to offer his attention, be a good listener, give advice only when asked for it, and will foster independence while he supports, can be a considerable factor in the adolescent's development into an effective adult.

## OTHER READINGS

Blaine, G. B., Jr., and McArthur, C. C., editors: Emotional Problems of the Student, New York, 1961, Appleton-Century-Crofts, Inc.

Erikson, E.: Childhood and Society, New York, 1950, W. W. Norton & Company.

Faegre, M. L.: The Adolescent in Your Family, Children's Bureau Publication #347, Washington, D. C., 1955, United States Department of Health, Education and Welfare.

Frank, M., and Frank, L. K.: Your Adolescent at Home and in School, New York, 1956, Viking Press, Inc.

Gallagher, J. R.: Medical Care of the Adolescent, New York, 1960, Appleton-Century-Crofts, Inc.

Gallagher, J. R., and Harris, H. I.: Emotional Problems of Adolescents, New York, 1958, Oxford University Press.

Josselyn, I. M.: The Adolescent and His World, New York, 1957, Family Service Association of America.

Mead, M.: Coming of Age in Samoa, New York, 1928, William Morrow & Co.

Williams, R. J.: Free and Unequal, Austin, 1953, University of Texas Press.

# TROPICAL PEDIATRICS

## *Histoplasmosis in an African child*

J. L. Lanceley, M.D., F.R.F.P.&S., D.T.M.&H.,* H. F. Lunn, M.B., F.R.C.S., and A. M. M. Wilson, B.M., Dip. Bact.

KAMPALA, UGANDA

IT HAS been claimed that there is in Africa a form of histoplasmosis differing in etiology and clinical pattern from the disease associated with infection with *Histoplasma capsulatum* in America and other parts of the world. The case to be described is of interest as it combines clinical features usually considered to belong to 2 distinct entities.

### CASE HISTORY

A male Muganda, 10 years of age, was admitted to Mulago Hospital on April 25, 1958, with a history of a painful swelling of the right ankle for 10 weeks. A provisional diagnosis of tuberculosis of the ankle was made. The swelling had come on gradually without fever and there was no history of trauma.

*From the Mulago Hospital and Departments of Surgery and Pathology, Makerere College Medical School, Kampala, Uganda.*

**Address, Mulago Hospital, Post Office Box 351, Kampala, Uganda.*

On admission the patient was thin and febrile. He had a temperature of 100° F., pulse 115, and a respiratory rate of 26 per minute (Fig. 1). He was poorly nourished and weighed only 41 pounds. He was pale, but liver and spleen were not enlarged. There was a generalized lymphadenopathy, the glands on the right side of the neck and the right inguinal and femoral groups being most prominent but not tender. The right ankle was swollen, fluctuant, and limited in its range of movement. Pus aspirated from this joint contained polymorphonuclear leukocytes and large thick-walled budding yeast forms measuring 10 to 15 $\mu$. No other organisms were seen and no growth on blood agar resulted. A tentative diagnosis of blastomycosis was made. While in the hospital he developed a dry cough, associated with whooping and vomiting. Physical examination of the chest revealed râles throughout both lungs. The chest film showed extensive bilateral, rather coarse, miliary opacities (Fig. 2).

**Fig. 1. Patient at the time of admission, May, 1958.**

On investigation the hemoglobin was 9.1 Gm. per cent and white blood cell count 14,500 cells per cubic millimeter (neutrophils 57 per cent, lymphocytes 37 per cent, eosinophils 1 per cent, and mononuclears 5 per cent). The Kahn and sickling tests were negative. The Mantoux tests were negative on 3 occasions. Sputum was negative for acid-fast bacilli and yeasts. Histoplasmin capsulatum skin testing was negative on 2 occasions.

As a provisional diagnosis of blastomycosis had been made, a course of stilbamidine intravenously was begun, 330 mg. being given in 10 days. The patient, who had become afebrile for the first time one day before the beginning of the course, developed remittent fever which persisted throughout the course and subsided within 48 hours of the last injection. After 5 injections had been given, a papular rash appeared over the trunk and flexor surface of the arms; the papules were lentiform, nonirritating, measuring about 4 by 7 mm. and appeared to be in the deeper part of the skin. This eruption gradually cleared. The cough began to abate 3 days after the completion of the course though it was still whooping in type. From this time the fever was only occasional and up to 100° F. Twenty-five milliliters of thick pus was aspirated from the right ankle on June 11. The overlying skin later broke down and formed a sinus. The aspirate contained cellular debris, pus cells, and many double-walled yeast cells, which were identified as *Histoplasma duboisii* by Dr. Jacqueline Walker.[1]

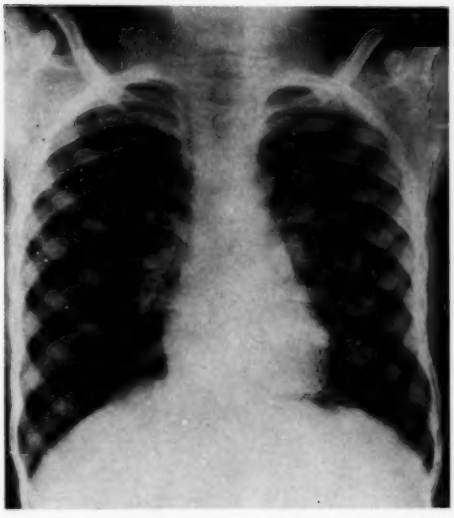


**Fig. 2. X-ray of the chest showing miliary opacities throughout both lung fields and enlarged hilar shadows, May, 1958.**

Fig. 3. Patient, June, 1959.

The patient became more comfortable and the cough disappeared.

Improvement persisted and the patient began to gain weight. At the end of July further crops of papules appeared in the skin. The glands in the neck increased in size and became tender and soft. The patient remained afebrile but went home at his parents' insistence on September 1. He was feeling well and weighed 46½ pounds. Plaster immobilization of the right ankle was recommended but refused. He continued to discharge pus through the sinus of his ankle.

The patient was seen again in June, 1959, at his home. He was found to be attending his normal class at school and was able to carry out physical training with the other boys. He walked with feet a little turned out but was not otherwise disabled. His weight had reached 51½ pounds, a gain of 10½ pounds within the previous 10 months. There were no open sinuses at the ankle but scars showed where they had been. He was clearly in good health as photographs show and was enjoying school (Fig. 3).

**Radiology.** In May, 1958, the film of the chest showed miliary opacities throughout both lung fields and enlarged hilar shadows, particularly on the left (Fig. 2).

Soft tissue swelling of the right ankle surrounded a bony lesion of the talus (Fig. 4). All bones of the tarsus showed gross osteoporosis. The head and neck of the talus were fragmented and their cortical outline was indistinct and incomplete. The skull showed a small defect in the frontal region. Generalized osteoporosis with loss of trabecular pattern was found in both tibiae and fibulae. Clearly defined osteolytic areas were seen in the right fibula, medial condyle of left tibia, and the distal end of the tibia (Fig. 5). Similar areas were seen in the right radius and left ulna. Scattered ill-defined areas of bone rarefaction were also visible in the spine, hands, and femora. All of these lesions showed similar loss of cancellous trabeculation and thinning of the cortex without new bone formation.

After one year the opacities in the chest film appeared little changed, regeneration

**Fig. 4.** Soft tissue swellings of the right ankle surrounding a bony lesion of the talus, May, 1958.

of the body of the talus had occurred and the head and neck had been almost completely absorbed (Fig. 6), the skull appeared normal, and the osteolytic areas in the other bones were no longer visible (Fig. 7).

**Mycology.** Two samples of pus were examined. The first was aspirated from the swelling over the ankle shortly after admission. In the direct smear many oval and round yeasts were seen measuring 10 to 15 $\mu$ in diameter. Most lay singly, but some were in pairs or threes end to end, the smaller terminal ones suggesting budding. Some contained a single round refractile body about 5 $\mu$ in diameter and had double walls (Fig. 8). A provisional diagnosis of blastomycosis was suggested. Culture of the pus on blood agar at 37° C. and on Sabouraud's medium at room temperature yielded no colonies of fungi or bacteria after 3 weeks.

In June, a second sample of pus was obtained from the ankle. The direct film showed the same features as in the first sample and several cultures were set up on blood agar and Sabouraud's medium. No growth occurred in Sabouraud's medium in

**Fig. 5.** Bones of both legs with osteolytic areas. A well defined area at the junction of the upper two thirds and the lower third of the right fibula, May, 1958.

**Fig. 6.** Showing regeneration of the body and absorption of the head and neck of the talus, June, 1959.

6 weeks at either room temperature or 37° C. No colonies appeared on the blood agar at 37° C., though films of the inoculated area suggested that the yeasts were multiplying, and subsequent subculture showed that the yeasts had remained viable.

Fungus did, however, grow from the original material on the blood agar plate left at room temperature. Colonies appeared after 4 weeks and were flat, grey, and stellate. Microscopically they consisted of septate hyphae bearing small conidia and large smooth chlamydospores. They became cottony at 6 weeks, but not until 2 months after inoculation was it possible to demonstrate the tuberculate chlamydospores diagnostic of Histoplasma (Fig. 9).

Examination of the 2 samples of sputum showed no Histoplasma or acid-fast bacilli.

**Fig. 7.** Bones of the right leg, June, 1959. Osteolytic areas no longer seen.

## REVIEW OF THE LITERATURE

In 1959 Van Laethem, Thys, and Vanbreuseghem[2] referred to 27 cases of infection with large yeast Histoplasma. The following cases have occurred in Africans and Europeans in Africa.

In 1936 Brumpt[3] discussed the case of an African soldier who presented with a tumor on the shoulder, first thought to be a cryptococcus infection but later judged to be due to *H. duboisii*.

In 1945 Catanei and Kervran[4] described an infection in a Sudanese presenting as an abscess over the maxilla. Large and small yeast forms, both intra- and extracellular, were demonstrated; recovery ensued. In 1947 Kervran and Aretas[5] reported a fatal case in an African Sudanese girl in whom the infection was widely disseminated.

In 1947 Friess and Delvoye[6] published a description of a Sengalese patient who died; he had bony lesions with sinuses and the parasite was demonstrated in the large yeast forms.

Since 1945 Duncan[7] has reported a number of cases, one in a European who had been resident in West Africa and the others in Africans.

In 1952 Dubois and colleagues[8] described a case occurring in a European in the Congo in whom manifestations were apparently limited to the testes and lymphatic nodes; recovery ensued.

In 1957 Vandepitte and associates[9] discovered a second case of the African form in the Congo. At autopsy *H. duboisii* was demonstrated in the tissues in both intra- and extracellular forms in many parts of the body.

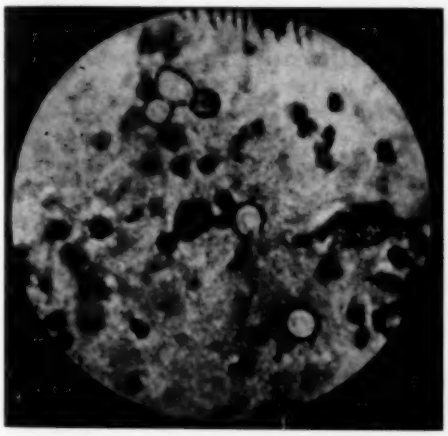


Fig. 8. Direct smear from the right ankle joint showing oval and round yeasts measuring 10 to 15 units in diameter.

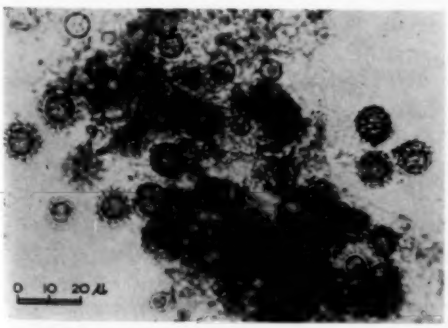



Fig. 9. Tuberculate chlamydospores on blood agar medium.

Clarke, Walker, and Winston[10] in 1953 and Symmers[11] in 1956 described cases occurring in young West Africans, in whom the manifestations were limited to the skin and subcutaneous tissues. The parasite was identified and the patients recovered.

In 1958 Camain and co-workers[12] investigated 7 new cases of the large yeast forms of histoplasmosis in French West Africa: in 4, bone alone was invaded; in 2, skin and subcutaneous tissues only; and in 1 fatal case, skin, lymphatic nodes and abdominal viscera. Six of the patients were Africans and the 1 European patient had yeast tissue forms measuring only 4.5 to 7.5 units described as intermediate forms.

In 1959 Van Laethem, Thys, and Vanbreuseghem[2] described a third case from the Congo. Skin, lymphatic nodes, bones, and viscera were involved and death ensued.

From the above publications it is clear that proved infections with large yeast Histoplasma are not always benign, but tend to fall into 2 main groups. In the first the lesions are limited to a single tissue (frequently the skin), and recovery can be expected. In the second, the lesions are multiple and involve several tissues often including the liver and spleen. A fatal outcome is almost invariable.

Although a number of cases of histoplasmosis has been reported in East Africa and South Sudan (Manson Bahr,[13] Dockeray,[14] Davies,[15] Jelliffe,[16] and Lunn[17]) the fungus was identified in only one (Lunn) and cultured in none. Ajello[18] has tabulated all reported cases of both forms of histoplasmosis which have occurred in Africa.

## DISCUSSION

**I. Mycologic.** In 1958 Vanbreuseghem[19] stated that the histopathologic differentiation of *H. duboisii* from *H. capsulatum* is the predominance of large yeast forms measuring between 10 and 15 units in diameter, presenting both inside and outside the histiocytes.

The validity of the distinction between these 2 forms of disease is not accepted by Symmers,[11] Moore,[20] Drouhet and Schwarz,[21] but Duncan[7] and Vanbreuseghem[19] and others have brought forward considerable evidence to support the view that an African pattern of histoplasmosis exists, caused by an organism differing from *H. capsulatum* in its appearance in the tissues and on culture.

*Results of experiments in animals.* In 1958 Duncan[7d] using strains of *H. capsulatum* and *H. duboisii* inoculated mice intravenously and intraperitoneally and observed results which do not in our opinion add significant support to the view that *H. duboisii* and *H. capsulatum* are distinct forms.

Five strains of *H. capsulatum* were used and only one old (1943) strain of *H. duboisii* in experiments designed to compare their effects. The histopathologic appearances were largely dependent on the channel of infection.

It is noteworthy that *H. duboisii* in these experiments produced progressive disseminated disease in mice, whereas in man it often produces localized and benign lesions.

Other authors, Catanei and Kervran[4] in 1945, Kervran and Aretas[5] in 1947, and Friess and Delvoye[6] in 1947 were able to produce large yeast forms in the tissues in animals infected with pus from cases with *Histoplasma duboisii*, but not with inoculates from cultures of *Histoplasma duboisii*. In 1956 Drouhet and Schwarz[21] and in 1957 Drouhet[22] produced large yeast forms in a hamster; both intra- and extra-cellular forms were present following inoculation with *H. capsulatum*. In 1957 Vandepitte[9] produced large and small tissue forms following intratesticular inoculations in guinea pigs with material from a patient dying from a *H. duboisii* infection. Large yeast forms have been observed in some American patients by Moore[20] in 1955, and have been seen in tissue explants from organs infected with *H. capsulatum* in an American patient by Schwarz[23] in 1953. De Monbreun[24] found large yeast forms in cultures inoculated with *H. capsulatum*.

From these results it is clear that either *H. capsulatum* or *duboisii* can give rise to large and small forms in the tissues and on culture. Taschdjian[25] has shown that the 2 strains show hyphal fusion in vitro and they are, therefore, unlikely to belong to 2 distinct species.

**II. Skin tests.** In 1958 Duncan[7] stated that a sample of histoplasmin from *H. duboisii* 1943 strain was antigenically identical with a standard preparation of histoplasmin prepared from *H. capsulatum*. Dr. Jacqueline Walker[1] states that although histoplasmin has been prepared from *H. duboisii*, the standardization of this material is still in the early stages and it is not generally available. This extract gives a cross reaction and detects *H. capsulatum*. It seems likely, although it has not yet been demonstrated, that the histoplasmin from *H. capsulatum* may give a similar cross reaction in patients infected with *H. duboisii*.

In 1956 Symmers[11] reported 2 benign cases with skin lesions of *H. duboisii* with large yeast forms in the tissues; one gave a positive histoplasmin skin reaction and one gave a negative reaction. In 1943 Robb-Smith[26] investigated a similar benign case with skin lesions with large yeast cells in the tissues and a negative histoplasmin skin reaction.

The case described in this article gave negative skin reactions on 2 occasions with the use of a standard preparation obtained from *H. capsulatum*.

In 1954 Ball and Evans[27] tested for histoplasmin sensitivity in 175 Uganda Africans and found 16 per cent positive to *H. capsulatum*. In 1954 Stott[28] found a sensitivity rate of 8.5 per cent to *H. capsulatum* in Kenya Africans.

**III. Clinical.** The patient described above presents several points of interest. He is the first patient with histoplasmosis to be proved by culture in East Africa. He is also the first patient with radiologic evidence of lung involvement in which the form of yeast is large celled. In no patient with such extensively disseminated disease has recovery been reported. This patient cannot, therefore, be included in either of the 2 groups of proved cases of large yeast histoplasmosis previously

described. In none of these patients was invasion of the lungs found, not even in the fatal cases. Involvement of lungs has hitherto been regarded as a feature of the disease caused by small yeast histoplasma. On the other hand, bone involvement, which is rare in small yeast disease, is present in this case and in several others from Africa. This case, therefore, forms a link not only between the 2 groups of large yeast infections previously referred to but also between the patterns of disease formerly attributed to 2 distinct causative organisms.

## SUMMARY

1. A case of large yeast histoplasmosis with disseminated lesions and a relatively mild illness ending in recovery is described.

2. The validity of the distinction between the American and African forms of histoplasmosis is questioned.

3. The evidence discussed would seem to be against a sharp distinction between 2 forms of causative agent. It is more likely that the differences noted in the manifestations of the disease are due to other factors. Among these must be included the mode of entry, dose of infective organisms, race of patient, climate, and degree of natural or acquired resistance.

We wish to thank the Permanent Secretary and Chief Medical Officer, Ministry of Health, Uganda, for permission to publish; Dr. Stephen Buck, Senior Pathologist, Uganda Medical Service, for examination of material; and Mr. K. W. Jones F.I.M.L.T. for culturing the fungus.

## REFERENCES

1. Walker, J.: Personal communication, 1958.
2. Van Laethem, R., Thys, A., and Vanbreuseghem, R.: Troisiene cas congolais d'histoplasmo—se par Histoplasma duboisii Vanbreuseghem 1952, Ann. soc. belge de med. trop. **39:** 319, 1959.
3. Brumpt, E.: Precis de Parasitologie, Paris, 1936, Masson et Cie. 1787.
4. Catanei, A., and Kervran, P.: Nouvelle mycose humaine observee au Soudan francais, Arch. Inst. Pasteur d' Algérie, **23:** 169, 1945.
5. Kervran, P., and Aretas, R.: Deux cas d' histoplasme observes au Soudan francais, Bull. Soc. path. exot. **40:** 270, 1947.
6. Friess, Lt. Col., and Delvoye, Med. Cdt.: A propos d'un aspect chirgical d'une mycose rare histoplasmose, Cahiers m. Union franc. **2:** 419, 1947.

7a. Duncan, J. T.: A Survey of Fungous Disease in Great Britain, Brit. M. J. **2:** 715, 1945.
b. Duncan, J. T.: Histoplasmosis in Great Britain, Brit. M. J. **2:** 1103, 1953.
c. Duncan, J. T.: A Unique Form of Histoplasmosis, Tr. Roy. Soc. Trop. Med. & Hyg. **40:** 364, 1947.
d. Duncan, J. T.: Tropical African Histoplasmosis, Tr. Roy. Soc. Trop. Med. & Hyg. **52:** 468, 1958.

8. Dubois, A., Janssens, P. G., Brutsaert, P., and Vanbreuseghem, R.: Un cas d'histoplasmose africaine. Avec une note mycologique sur Histoplasma duboisii n.sp., Ann. soc. belge de med. trop. **32:** 569, 1952.
9. Vandepitte, J., Lamote, J., Thys, A., and Vanbreuseghem, R.: Deuxieme cas congolais d'histoplasmose par Histoplasma duboisii Vanbreuseghem, Ann. soc. belge de med. trop. **37:** 515, 1957.
10. Clarke, G. H. V., Walker, J., and Winston, R. M.: African Histoplasmosis, J. Trop. Med. & Hyg. **56:** 277, 1953.
11. Symmers, W. St. C.: Localised cutaneous histoplasmosis, Brit. M. J. **2:** 790, 1956.
12. Camain, R., Berte, M., Kledstad-Sillonville, F., Mafart, J., Vilasco, J. A., and Drouhet, E.: Sept nouveaux cas d'histoplasmose observes en A.O.F., Bull. Soc. path. exot. **51:** 83, 1958.
13. Manson-Bahr, P. E. C.: Histoplasmosis in East Africa, East African M. J. **35:** 625, 1958.
14. Dockeray: in Manson Bahr: East African M. J. **33:** 628, 1958.
15. Davies, P.: A Fatal Case of Histoplasmosis Contracted in Kenya, East African M. J. **34:** 555, 1957.
16. Jelliffe, D. B.: Histoplasmosis of Darling, J. Trop. Med. & Hyg. **52:** 177, 1949.
17. Lunn, H. F.: A Case of Histoplasmosis of Bone in East Africa, J. Trop. Med. & Hyg. **63:** 175, 1960.
18. Ajello, L., Manson Bahr, P. E. C., and Moore, J. C.: Amboni Caves, Tanganyika, a New Endemic Area for Histoplasma Capsulatum, Am. J. Trop. Med. **9:** 633, 1960.
19. Vanbreuseghem, R., editor: Mycoses in Man and Animals, London, 1958, Sir Isaac Pitman & Sons, Ltd.
20. Moore, M.: Morphologic Variation in Tissue of Organisms of Blastomycoses and of Histoplasmosis, Am. J. Path. **31:** 1049, 1955.
21. Drouhet, E., and Schwarz, J.: Comparative Studies With 18 Strains of Histoplasma. Morphology in Tissues and Virulence of African and American Strains, J. Lab. & Clin. Med. **47:** 128, 1956.
22. Drouhet, E.: Quelques aspects biologiques et mycologiques de l'histoplasmose, Semaine hop. Paris **5:** 1299, 1957.
23. Schwarz, J.: Giant Forms of Histoplasma Capsulatum in Tissue Explants, Am. J. Clin. Path. **23:** 898, 1953.
24. De Monbreun, W. A.: The Cultivation and

Cultural Characteristics of Darlings Histoplasma Capsulatum, Am. J. Trop. Med. **14:** 93, 1934.
25. Taschdjian, C. L.: Hyphal Fusion Studies on Histoplasma Capsulatum and Histoplasma Duboisii Vanbreuseghem 1952, Mykosen **2:** 1, 1959.
26. Robb-Smith, A. H. T.: Cited by Duncan.[7a]
27. Ball, J. D., Evans, P. R.: Histoplasmin Sensitivity in Uganda, Brit. M. J. **2:** 848, 1954.
28. Stott, H.: Histoplasmin Sensitivity and Pulmonary Calcification in Kenya, Brit. M. J. **1:** 22, 1954.

**Erratum.** In the article, "Pyridium-induced Methemoglobinemia" by Sand and Edelman (J. PEDIAT. **59:** 845, 1961) reference 5 is incorrect. It should have been: Lees, M. H., and Jolly, Hugh: Severe Congenital Methaemoglobinaemia in an Infant, Lancet **2:** 1147, 1957.

# MEDICAL PROGRESS

## *Some remarks on hemoglobinopathies with particular reference to thalassemia*

J. H. P. Jonxis, M.D.* **

GRONINGEN, NETHERLANDS

MODERN medical science is attempting to find out why a protein that is built from a fixed sequence of a known number of amino acids has certain properties. We would also like to know what differences there are between normal and abnormal proteins and why a particular anomaly changes the biologic properties of a protein. We do not yet know why an abnormal reconstructed protein causes a disease in its carrier. What is the connection between a postulated mutation and the synthesis of one or more abnormal proteins? How is evolution reflected in the structure of one special protein? For instance, what are the structural similarities and differences between the hemoglobins of different species?

Recent discoveries have made it possible to answer some of these questions and to answer to a certain extent for the protein, hemoglobin. This accomplishment has been achieved by the work of different investigators whose approaches to the problem have varied markedly.

Hemoglobin has a molecular weight of about 66,000. The molecule consists of 2 pairs of different polypeptide chains, called alpha and beta chains.[1] Each chain has a molecular weight of about 16,500. The lengths of the alpha and beta chains are about equal. The amino acids of the polypeptide chains are helically coiled over the major parts of the chains; this regular arrangement must be disturbed at those places where the polypeptide chain rounds a corner because each chain is folded in a special manner. The heme group lies in a loop of the polypeptide chain and is attached by a histidine group.[2] The forces that keep the polypeptide chains together are relatively weak. In a concentrated urea solution, for instance, the hemoglobin molecule is split into 2 pairs of chains. Recombination of these pairs of chains is possible under certain conditions.[3] In this way it is possible to make new forms of hemoglobin; for instance, one

*From the Department of Pediatrics, University of Groningen, Netherlands.*

**Lecturer of the Journal of Pediatrics Educational Foundation, autumn, 1960.*

***Address, Department of Pediatrics, State University, 59 Oostersingel, Groningen, Netherlands.*

**Fig. 1.** Fingerprint of Hb. $A_1$. Numbering system of the tryptic peptides according to Ingram.

may recombine human alpha chains with beta chains of an animal hemoglobin.[4] The blood of the normal adult contains one major fraction (Hb. $A_1$) together with smaller amounts of other hemoglobins. The most important of these minor fractions is the hemoglobin fraction called $A_2$. It has a higher electrophoretic mobility at pH 8.6 and has somewhat higher affinity for oxygen than Hb. $A_1$. It is present in the blood in a percentage of 2 per cent. A third fraction is Hb. $A_3$ which has a somewhat slower electrophoretic mobility than Hb. $A_1$ and is present in the blood in a concentration of 1 per cent. Traces of fetal hemoglobin, less than 0.5 per cent, have been found in the blood of normal adults, and it is likely that minute amounts are present continuously in the blood of most of us (Table I).

The molecular structures of these four hemoglobins have been practically worked out. We know much less, however, about the physiologic activities of these closely related proteins. Hb. $A_2$ has a somewhat higher affinity for oxygen,[5] but it occurs in such small amounts that it does not affect the total affinity of the blood for oxygen. Much work has been done on the affinity of fetal hemoglobin for oxygen. In most mammals the affinity of fetal hemoglobin for oxygen is greater than that of the adult hemoglobin of the same animal. This property is likely to be useful in the light of the difficult oxygen transport before birth. In the human the affinity of the fetal red blood cells for oxygen is increased compared with those of the adult. This, however, contrary to what has been found in the animal, is not caused by a greater affinity for oxygen of the hemoglobin of the newborn, the oxygen dissociation curve of human fetal hemoglobin being the same as that of human adult hemoglobin.[6]

Hemoglobins $A_1$ and $A_2$ and fetal hemoglobin have the same alpha chains; their beta chains, however, are different.[7] These differences in beta chains are due to differences in the amino acid composition of the polypeptide chain. This can be beautifully demonstrated by the so-called fingerprint technique of Ingram.[8]

This fingerprint technique is based on the separation of peptides obtained by a tryptic digest of the hemoglobin or of the separate chains. Trypsin splits the polypeptide chains into peptides at the amino acids, arginine and lysine. These peptides are separated from each other with chromatographic and electrophoretic methods and stained with ninhydrin. Twenty-three different peptides can be detected in the fingerprint of Hb. $A_1$ (Fig. 1). Special color reactions make it

possible to detect the presence of a number of special amino acids in these peptides. This allows one to differentiate peptides which have the same mobility in the fingerprint but which contain one different amino acid. By application of this method, different investigators have shown that the alpha chains of the hemoglobins $A_1$ and $A_2$ and fetal hemoglobin are identical, but that their beta chains are distinct. The beta chain of fetal hemoglobin, which is called a gamma chain,[9] differs in 7 of its 15 peptides from the beta chain of adult hemoglobin. It is noteworthy that the gamma chains of all investigated mammals contain isoleucine. The beta chains of the hemoglobin of adult animals, with the exception of the rabbit and the hare, contain no isoleucine.

The fingerprint of the beta chain of the Hb. $A_2$, which is called the delta chain, differs from the beta chain of Hb. $A_1$ to a smaller extent. Here only 4 peptides have other places in the fingerprints (Fig. 2).[10]

A hereditary variation of Hb. $A_2$, called $B_2$, is known. The carriers of this Hb. $B_2$ do not show anomalies in their Hb. $A_1$. Such anomaly might be expected when the beta and delta chains were formed under the influence of the same genes. This is a strong argument for the hypothesis that the synthesis of the delta chain is, at least partially, under the influence of special genes.

**Table I.** The concentrations of different hemoglobin forms in the blood of the normal adult

| $A_1$ | $A_2$ | $F$ |
|---|---|---|
| 97.9% | 2% | 0.1% |
| $\alpha_2\ \beta_2$ | $\alpha_2\ \delta_2$ | $\alpha_2\ \gamma_2$ |

**Table II.** The activity of different hemoglobin fractions after administration of radioactive chromium ($Cr^{51}$)

| | *(cpm./mg. Hb.)* | | | |
|---|---|---|---|---|
| | $A_3$ | $A_1$ | $A_2$ | $F$ |
| Adult | 206 | 1 | 11 | |
| Baby (4 weeks old) | 89 | 7 | | 1 |

On the other hand, the great similarity of the beta and delta chains makes it likely that for the greater part of their synthesis the same ribonucleic acid template is used. Also, the synthesis of fetal hemoglobin, at least that of the gamma chains, is regulated by special genes. Again hereditary anomalies of the synthesis of the gamma chains have been found.

Hb. $A_3$ has a special place. It occurs mainly in the aged red blood corpuscle. When erythrocytes are incubated with chromium[51], the chromium is found to attach itself preferentially to Hb. $A_3$ (Table II).[11]

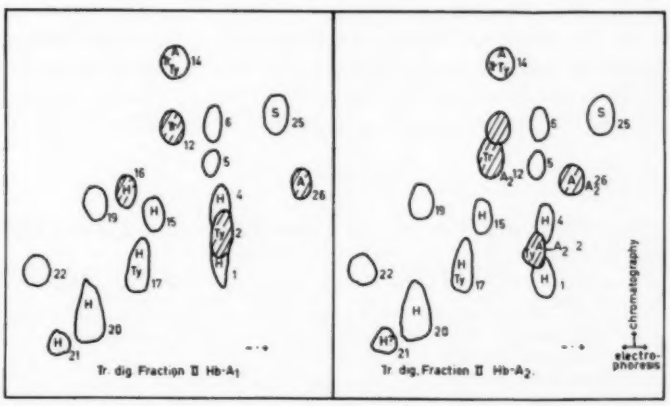



**Fig. 2.** Comparison of the beta chains and the alpha chains of hemoglobins $A_1$ and $A_2$. The peptides that are different are shaded.

**Table III.** The different hemoglobin component of fetuses

| *Age (weeks)* | | *Cord blood* | | |
|---|---|---|---|---|
| | | $A_{1+3}$ | $F_1$ | $A_2$ |
| Full-term | 36 | 26.0 | 73.7 | 0.3 |
| Premature | 28 | 13.5 | 86.0 | 0.4 |
| Fetus | 20 | 8.4 | 90.8 | 0.1 |
| Fetus | 18 | 7.3 | 91.2 | 0 |

The fingerprint of Hb. $A_3$ is the same as that of Hb. $A_1$ with the addition of one extra peptide which we found to contain glutathione.[12] Since Hb. $A_3$ is found especially in the older erythrocytes, it may be a first step in the breakdown of the hemoglobin. The quantities in which Hb. $A_1$ and $A_2$ and fetal hemoglobin occur in the blood depend on the age of the carrier and on hereditary factors. Most acquired diseases are of no influence. Tumors, such as molar pregnancy, some forms of leukemia, and aplastic anemia, may cause, however, a rise of the concentration of fetal hemoglobin in the blood of the adult. Alpha and gamma chains are the predominant chains synthesized before birth, and fetal hemoglobin is thus the predominant hemoglobin. However, from the earliest stage onward, some beta chains, thus adult hemoglobin, are formed. In the youngest human fetuses we were able to examine (18 weeks) adult hemoglobin could already be demonstrated (Table III). The quantity of Hb. $A_2$ formed before birth is small. We succeeded, however, in finding it in the blood of 20-week-old fetuses. It appeared in part to be synthesized to Hb. $A_1$. At birth the Hb. $A_2$ percentage is still less than 1.

Halbrecht and Klibanski[13] and Drescher and Künzer[14] have described a special form of young fetal hemoglobin in the human. We were not able to confirm their observations. The youngest fetuses we were able to examine, however, were 15 weeks old and the possibility exists that this special hemoglobin occurs in still younger fetuses. Recently, a special young fetal hemoglobin in very young human fetuses has been described by Butler and associates[15] and by Flynn, Butler, and Beaven.[16]

Even before birth the quantity of adult hemoglobin increases at the expense of the fetal hemoglobin showing that there is a change from the synthesis of gamma chains to that of beta chains. This shift occurs before birth and is not the result of the end of intrauterine life. The increased breakdown of erythrocytes in patients with hemolytic anemia resulting from an antagonism between blood groups causes a decrease in the fetal hemoglobin. The main cause of this phenomenon is the breakdown of older erythrocytes, which have a higher percentage of fetal hemoglobin, and their replacement by new erythrocytes, which have a lower percentage of fetal hemoglobin. It is possible to demonstrate that at birth the fetal hemoglobin percentage is higher in the older erythrocytes than in newly formed ones.[17] During the second half of the first year of life approximately 5 per cent fetal hemoglobin is present, indicating that there is still increased production of this hemoglobin during this period. After the first year of life the percentage of fetal hemoglobin drops still lower and its detection becomes difficult (Fig. 3). It is likely, however, that small

**Table IV.** Comparison of the amounts of different hemoglobin components in different cases

| *Disease* | $A_{1+3}$ | $A_2$ | $F$ | $S$ | $C$ |
|---|---|---|---|---|---|
| Normal adults | 97.5 | 2 | 0 | 0 | 0 |
| Heterozygous Hb. S | 63 | 1.5 | | 34.5 | |
| Heterozygous Hb. C | 66 | | | | 33.5 |
| Homozygous Hb. S | | 2.5 | 10 | 87 | |
| Homozygous Hb. C | | 9 | 2 | | 88 |
| Hb. S + Hb. C | | | 3.5 | 52.5 | 43.5 |

**Table V.** The hemoglobins that might be expected in the blood of the double heterozygous carrier of the Hb. S and I gene

| $A_1$ | $I$ | $S$ | $X$ |
|---|---|---|---|
| $\alpha_2\ \beta_2$ | $\alpha_2^I\ \beta_2$ | $\alpha_2\ \beta_2^S$ | $\alpha_2^I\ \beta_2^S$ |
| $A_2$ | $A'_2$ | $F$ | $F'$ |
| $\alpha_2\ \delta_2$ | $\alpha_2^I\ \delta_2$ | $\alpha_2\ \gamma_2$ | $\alpha_2^I\ \gamma_2$ |

amounts are synthesized during the entire life span. We may, therefore, assume that alpha, beta, gamma, and delta chains are also synthesized throughout life, although in amounts that differ sharply with age.

Hereditary aberrations of hemoglobin synthesis are now known to be localized in the four different chains. The most common are the anomalies in the beta chain. To this group hemoglobins S, C, and E belong. Fingerprint studies show that the anomaly in both hemoglobins S and C can be localized in peptide 4 of the beta chain. One glutamic acid that is normally present in this peptide is replaced by valine in Hb. S and by lysine in Hb. C (Figs. 4 and 5).[18] In Hb. E the anomaly is found in peptide 26.[18] Here once more, glutamic acid is replaced by lysine. Ingram's discovery that the difference between the hemoglobins A, S, and C is localized to one place in the polypeptide chain is in agreement with the results of genetic studies of affected families, which show that the genes for the regulation of the synthesis of hemoglobins S and C are allelic.

Family studies also make it likely that the Hb. E gene is allelic with the genes of hemoglobins S and C. The finding, however, that the anomaly in Hb. E is localized in another peptide (No. 26) of the beta chain does not fit in this hypothesis. It is more probable that the locus of the Hb. E gene is very close to the locus of the genes for hemoglobins S and C.

Synthesis of an abnormal component of hemoglobin appears to proceed at a slower rate than that of normal components. In a heterozygous person an increased synthesis of Hb. $A_1$ will compensate for the decreased formation of the abnormal protein. In a homozygous person this escape route does not exist because he cannot make Hb. $A_1$. In such an individual the synthesis of Hb. F or in some cases of Hb. $A_2$ is increased. A person who is heterozygous for Hb. S, a beta chain anomaly, will show Hb. S $\alpha_2\beta_2^s$, Hb. $A_2$ $\alpha_2\delta_2$, and F $\alpha_2\delta_2$ in the blood (Table IV).

When there is a disturbance in the synthesis of the alpha chains, for instance Hb. I, we shall find in a person who is heterozygous for this anomaly Hb. $A_1$, Hb. I, Hb. $A_2$, and, because of the anomaly of the alpha chain, also an abnormal $A_2$. Recently we were able to investigate the blood of a person who was heterozygous for the I gene. We were able to demonstrate the following hemoglobins in the blood: 76 per cent Hb. $A_1$, 20 per cent Hb. I, 3 per cent Hb. $A_2$, and an unknown component in a concentration of 0.8 per cent (Fig. 6). A fingerprint was made of this component. It showed the characteristics of Hb. $A_2$ but also those of Hb. I, i.e., tryptophane in peptide 23.

In the blood of such a patient we find 4 hemoglobin components: Hb. A $\alpha_2\beta_2$, Hb.

**Table VI.** Curaçao

| | *Total Negro population* | | | *District III* | | |
|---|---|---|---|---|---|---|
| | *No.* | *%* | *Average age in years* | *No.* | *%* | *Average age in years* |
| AA | 652 | 83 | 34 | 296 | 85 | 35 |
| AS | 68 | 9 | 35 | 18 | 5 | 37 |
| AC | 57 | 7 | 36 | 28 | 8 | 39 |
| SS | 7 | 1 | 19 | 1 | | 18 |
| SC | 3 | 0 | 28 | 3 | 1 | 28 |

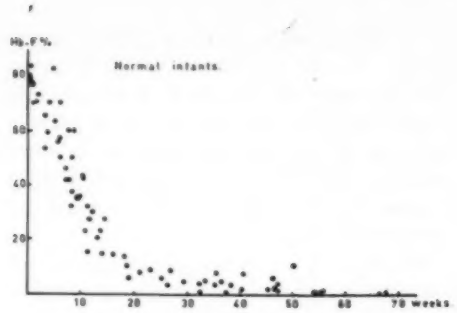



**Fig. 3.** The fetal hemoglobin percentages in the blood of children of different ages.

I $\alpha_2^I\beta_2$, Hb. $A_2$ $\alpha_2\delta_2$, and Hb. $A_2^I$ $\alpha_2^I\delta_2$. We may expect that the fetal hemoglobin of such a patient was also abnormal.

The situation is quite complicated in a person who is heterozygous for an abnormality in both the alpha and beta chains, for instance, a person who is a carrier of Hb. I and S. According to the theory such a person should synthesize not less than 8 hemoglobins. Some of them will occur in very small amounts (Table V). Moreover, the electrophoretic mobility of Hb. $alpha_2^I$ $beta_2^S$ will be about the same as that of Hb. $A_1$, because one of its components has a higher and the other a lower electrophoretic mobility at pH 8.6 than has Hb. $A_1$.

Double heterozygotes for anomalies in both alpha and beta chains are very rare, but they are of considerable theoretical interest. Individuals with 4 hemoglobins in their erythrocytes have recently been described by Raper and colleagues[18a] and Baglioni and Ingram.[19] In recent years anomalies in the gamma chain of fetal hemoglobin have been discovered. They can only be detected in the blood of young infants; the anomalies produced are known as the hemoglobins of Alexandra[20] and Fessas.[21]

It is noteworthy that under certain conditions 4 similar chains may form one hemoglobin molecule. Thus, 4 beta chains form Hb. A[22] and 4 gamma chains make up Hb. Bartholomews[23] which occurs in some newborn infants. One might assume that the formation of these hemoglobins was caused by a lack of alpha chains. The fact, however, that 4 beta[S] chains have the tendency to form Hb. Augusta[24] in patients with sickle cell anemia is not in agreement with the supposition, for in a patient with sickle cell anemia the synthesis of alpha chains is unaffected. The abnormal beta[S] chains have the tendency to congregate together. It should be noted that Hb. H and Hb. Bartholomews are found in families in which thalassemia occurs.

Carriers of Hb. S and of Cooley's anemia are rather common in certain districts. This is the more noteworthy because there is a constant loss of the genes for these hemoglobins, since 1 in 4 children of a family in which both parents are heterozygous carriers of the genes dies before he can produce offspring. This will cause a decrease of the gene frequency. It is unlikely that a high mutation rate compensates for the loss of abnormal genes. It is more likely that the high frequency is the result of a form of balanced polymorphism, the heterozygous carrier having an advantage over the normal individual in some other respect.

In recent years the theory has been advanced that both sickling and thalassemia give a degree of protection against malaria, for in many countries where malaria was endemic, Cooley's anemia and sickle cell anemia are common. Some years ago I did some work that fits well in this hypothesis.

Two centuries ago Negroes from Ghana, where carriers of Hb. S and Hb. C are common, were transported to 2 places in the New World. In one of these places, Curaçao, malaria was very rare; in the other place, Surinam (Dutch Guyana), it was, as in Ghana, very common. In Curaçao this group of Negro immigrants is still living in the western part of the island, district III, and is not mixed with a second wave of Negro immigration of recent years. In Surinam, groups of Negroes fled the inland during the numerous wars and uprisings in the seventeenth and eighteenth centuries. They formed new tribes, Bush Negroes, and lived a primitive life isolated from the rest of the world. Both groups have lived now for about

**Table VII.** Surinam

| | *Kabel* | | | *Moengo* | | | *Stoelmans eiland* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *No.* | *%* | *Average age in years* | *No.* | *%* | *Average age in years* | *No.* | *%* | *Average age in years* |
| AA | 401 | 77 | 22 | 126 | 73 | 28 | 234 | 85 | 26 |
| AS | 87 | 16.8 | 20 | 35 | 20 | 28 | 31 | 11.3 | 19 |
| AC | 27 | 5.2 | 25 | 8 | 1 | 35 | 9 | 3.3 | 21 |
| SS | 1 | 0.2 | 14 | 2 | 1 | 16 | 1 | 0.4 | 2 |
| SC | 3 | 0.5 | 15 | 1 | 0.5 | 31 | 0 | | |

200 years in their new surroundings. The differences in the frequency of the hemoglobins S and C genes are very likely to be the result of the differences of circumstances during these centuries, because the frequency of these genes must have been the same in both groups in the original immigrants.

A comparison of the frequency of hemoglobins S and C in Ghana, Surinam, and Curaçao, therefore, may give useful information. Figures for Ghana have been published by Edington and Lehmann.[25] They have found a higher percentage of Hb. C carriers in inland areas and a higher frequency of Hb. S carriers in the coastal region. However, we do not know how the situation was 200 years ago, or if the immigrants came from the northern parts of the country or from the coastal belt. We have collected figures in Surinam and Curaçao, testing more than 1,000 people in each place (Fig. 8, Table VI).

One might expect that the numbers of carriers of the sickle cell trait would be significantly lower in Curaçao, because of the absence of malaria, than in Ghana, whereas the number of Hb. C carriers would be only slightly less. In Surinam, on the other hand, we may expect a percentage of Hb. S carriers approximating that found in West Africa. What, in fact, are the findings? In Curaçao we obtained blood samples from 790 pure Negroes, 349 of whom lived in a remote part of the island which had not received new immigrants. (The population of Curaçao has risen rather sharply lately.) In the

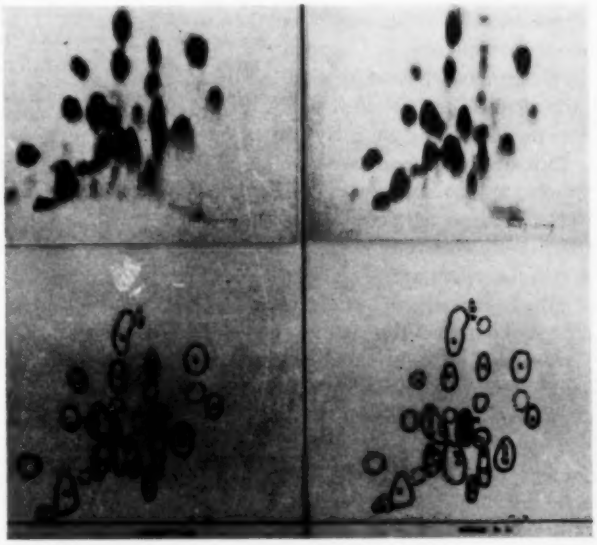


**Fig. 4.** The fingerprint of the tryptic digest of the hemoglobins $A_1$ and S. The differences (peptide 4) are shaded.

| | |
|---|---|
| Hb-A | VAL - HIST - LEU - THR - PRO - [GLU] - GLU - LYS |
| Hb-S | VAL - HIST - LEU - THR - PRO - [VAL] - GLU - LYS |
| Hb-C | VAL - HIST - LEU - THR - PRO - [LYS] - GLU - LYS |

**Fig. 5.** The amino acid sequence in peptide 4 in the hemoglobins $A_1$, S, and C.

remote area, district III, 8.2 per cent of the population have Hb. C in their blood and 5.2 per cent have sickle cell hemoglobin. These figures are lower for Hb. S than the average of the Ghana values (North Ghana Hb. S 12 per cent, South Ghana 22 per cent; for Hb. C these figures are respectively 15 per cent and 11 per cent). The fact that the proportion of Hb. C carriers is high compared with that of Hb. S carriers is a strong indication that the original Curaçao Negroes came from Ghana, because Ghana is the only country where Hb. C is found so frequently. It is noteworthy that the total number of carriers of both anomalies is lower in Curaçao than on the Gold Coast. It is likely that these percentages have gone down since the arrival of the original immigrants. The most obvious explanation is that this may be due to the absence of malaria in Curaçao.

In Surinam we were able to make investigations in 3 groups of Bush Negroes. The total number of the Bush Negroes of Surinam is estimated to be about 25,000 of whom we were able to investigate 966 (Fig. 9, Table VII). The percentages found in 2 of the groups were about the same. The percentages of Hb. S carriers are 17 and 20, respectively; of Hb. C carriers, 5.2 and 4.6, respectively. It is striking that the percentages of Hb. S carriers are about 3 times as high as that found in Curaçao and only somewhat lower than those found in West Africa. This is in agreement with the malaria theory. The number of Hb. C carriers, on the other hand, is significantly lower than that in Curaçao. This may be explained by the possibility already mentioned that the Negroes of Surinam came from a somewhat more extended part of West Africa than the Curaçao Negroes.

In the third small group the percentage of Hb. S carriers was only 11 and that of Hb. C 3.3. One might have expected a higher S percentage in this group. It is likely that this deviation is the result of a genetic drift in a small tribe which originated about 200 years ago in a restricted number of runaways. Except for the values in this small group, the findings are in good support for the malarial theory.[26]

Cooley's or Mediterranean anemia or thalassemia is common in certain groups of the Mediterranean countries, in the Near East, in middle and southeast Asia, and in some parts of Africa. Sporadic cases have been reported in the autochthonous population of Western Europe.

Two forms can be distinguished: thalassemia minor, the disease of the heterozygous carriers, and thalassemia major, the disorder of the homozygous carriers of the gene. Thalassemia major is such a severe disease that most affected persons die in childhood. Both parents of a patient with thalassemia major are carriers of the Cooley gene and 1 in 4 of their children will die of this disease. Thus the number of individuals with thalassemia minor is greater than one might expect from the frequency of children with thalassemia major.

The line between thalassemia major and

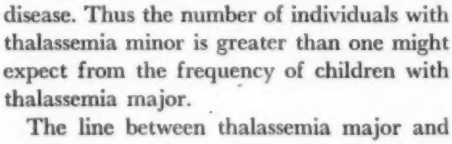


**Fig. 6.** The different Hb. fractions in a Hb. I carrier. Carboxy-methylcellulose-chromatography.

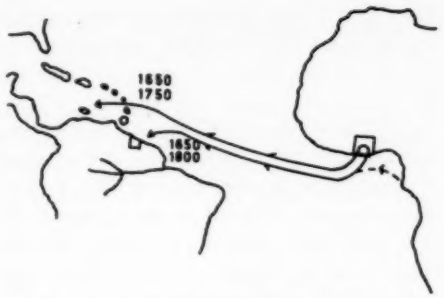



**Fig. 7. The transport of Negroes from Ghana to Curaçao and Surinam in the seventeenth and eighteenth century.**

minor is not always easy to draw. Cases of intermediate severity are called thalassemia intermedia. In these cases only family studies can make it clear whether the affected person is homozygous or heterozygous for the gene.

Up until now no special thalassemia hemoglobin has been found. This makes it difficult to decide whether there are different genes for Cooley's anemia as has been postulated by different authors.[27] Such a hypothesis has the advantage that it allows one to explain the differences in severity which we encounter in Cooley's anemia. The problem becomes still more complicated by the fact that the clinical picture of the double heterozygous carrier of both the Cooley's gene and the Hb. E gene is the same as that of Cooley's anemia. The presence of Hb. E, however, in the blood of these patients distinguishes them from pure Cooley's anemia. Once more it is important to examine the blood of other members of the patient's family.

Microcytosis and variation in size among erythrocytes typify Cooley's anemia. The hemoglobin concentration in the erythrocyte is less than normal. The anomalies are much greater in thalassemia major than in thalassemia minor. In thalassemia major normoblasts are found in the blood smear. Although the number of reticulocytes is high, the average life span of the erythrocytes is only moderately shortened, and the anemia is severe because of a defect in hemoglobin synthesis. In thalassemia major the fetal hemoglobin is increased and in thalassemia minor the percentage of Hb. $A_2$ is about twice its normal value in nearly all cases.[28] The latter fact is of great practical value because sometimes it is otherwise difficult to differentiate thalassemia minor from iron deficiency anemia. In a number of cases of thalassemia minor there is a moderate increase of the concentration of fetal hemoglobin. This is, however, not only present in thalassemia minor but may also be found in other hemoglobinopathies. Moreover, there is a group of West African Negroes in which the fetal hemoglobin concentration remains high without any further hematologic abnormality. Both the presence of fetal hemoglobin and the increased concentration of Hb. $A_2$ are in agreement with the hypothesis that in Mediterranean anemia there is a disturbance in the formation of the beta chains.

Hb. H (beta 4) that occurs in patients with thalassemia can be compared with the occurrence of Hb. Augusta in sickle cell anemia. Two possibilities are suggested: (1) the formation of beta chains is decreased, or (2) abnormal beta chains are synthesized at a low rate. In the latter hypothesis it is assumed that abnormal beta chains are formed, but this anomaly has not yet been demonstrated.

There are some other anemias in which the percentage of fetal hemoglobin is in-

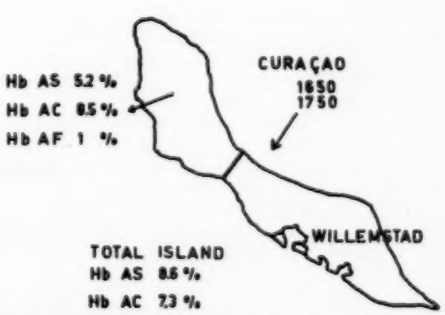



**Fig. 8. The frequency of carriers of the hemoglobins S and C in Curaçao.**

Fig. 9. The frequency of carriers of the hemoglobins S and C in Surinam.

creased. In recent years my co-workers and I were able to investigate the blood of a number of patients with Fanconi's anemia. In all these cases we found a fetal hemoglobin concentration between 5 and 25 per cent. In the parents' blood no fetal hemoglobin could be detected.

Recently we had the opportunity to examine a family in which an anemia occurred that has many features in common with Fanconi's anemia. The affected members were a grandfather, a father, and his little daughter. Both father and daughter were anemic; the hemoglobin values were 9 Gm. per 100 ml. The erythrocytes were large and numbered about 2,400,000 per cubic millimeter. The intracellular hemoglobin concentration was about normal. The fetal hemoglobin concentration was about 5 per cent and the Hb. $A_2$ concentration was normal (2.3 per cent). The numbers of leukocytes and thrombocytes were low. This anemia differs from thalassemia because of the low Hb. $A_2$ concentration and because of the macrocytosis. It differs from Fanconi's anemia because of the good prognosis and the lack of multiple skeletal malformations.

To conclude I would like to report an observation in another family. It concerns a Papuan family in which some members showed the clinical picture of Cooley's anemia. Some time ago 2 Papuan children were admitted to the Hospital of Hollandia, New Guinea.[29] They showed the clinical picture of severe Cooley's anemia. There was a microcytosis, the shape of the erythrocytes was irregular, and some target cells were present. The number of reticulocytes was high, and normoblasts were numerous. The liver and spleen were enlarged and the x-ray of their skulls showed the typical picture of a hemolytic anemia. No malaria parasites could be demonstrated in the blood, which is exceptional for children of their age in that population.

The anemia had not improved following the normal treatment for deficiency anemia. The fetal hemoglobin concentration in the children's blood was about 75 per cent, and the Hb. $A_2$ concentration only 0.3 per cent. No Hb. $A_1$ could be detected. There was, however, another component present that

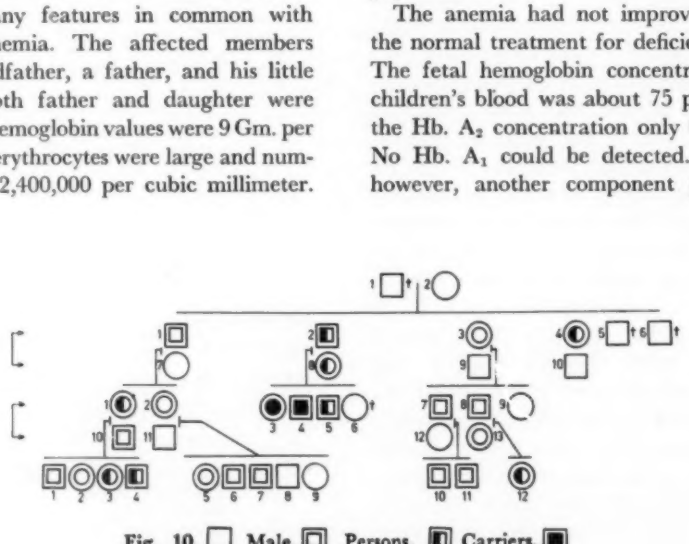


Fig. 10. □ Male. ▣ Persons. ◧ Carriers. ■ Homozygous. ○ Female. ◎ Investigated. ◐ Lepore Hb. ◉ Carriers Lepore Hb.

could be identified as Lepore hemoglobin. In the parents' blood the Hb. $A_2$ concentration was low; the concentration of Lepore hemoglobin was 12 per cent, and the remaining hemoglobin was Hb. $A_1$. We were able to investigate the blood of several members of both the father's and mother's families (Table VI, Fig. 10). In each family heterozygous carriers of Lepore hemoglobin were detected. Since both parents had Lepore hemoglobin it may be concluded that their 2 affected children were homozygous for the Lepore gene, particularly since no Hb. $A_1$ could be found in the blood. We did not find any carrier of the Cooley's gene in these families nor does this gene occur in other Papuan families as far as is known. We must, therefore, assume that homozygosity for the Lepore gene gives a clinical picture that is identical with that of Cooley's anemia.

Gerald[30] reported that patients who are doubly heterozygous for both Lepore and Cooley's genes show the clinical picture of thalassemia. It is remarkable that the fingerprint of Lepore hemoglobin is the same as that of Hb. $A_2$. At least, we were not able to detect any difference. Still Lepore hemoglobin is not identical with Hb. $A_2$, for its electrophoretic mobility is different. We know that the anomaly of Lepore hemoglobin is localized in the beta chain and that the Lepore beta chain must have a structure that is quite similar to the delta chain of Hb. $A_2$. It is interesting to note that homozygosity for Lepore gene, which gives a beta chain anomaly, is responsible for the clinical picture of thalassemia. This might be an indication that in thalassemia there is also a still undiscovered anomaly in the beta chain.

Hemoglobin is the only intracellular protein readily available for investigation. Therefore, we know more about the hereditary anomalies in this protein than in any other. It is very likely, however, that similar patterns exist in several other intracellular proteins. This makes the study of abnormal hemoglobins more than the collection of rare stamps with which it is sometimes compared.

## REFERENCES


1. Rhinesmith, H. S., Schroeder, W. A., and Pauling, L.: The N-Terminal Amino-Acid Residues of Normal Adult Human Hemoglobin: A Quantitative Study of Certain Aspects of Sanger's DNP-Method, J. Am. Chem. Soc. **79:** 609, 1957.
2. Perutz, M. F., et al.: Structure of Hemoglobin A, Nature **185:** 416, 1960.
   Kendrew, J. C., et al.: Structure of Hemoglobin A, Nature **185:** 422, 1960.
3. Robinson, E., and Itano, H. A.: Properties and Inheritance of Haemoglobin by Asymmetric Recombination, Nature **184:** 1468, 1959.
   Assymetric Recombination of Alkali-Dissociated Hemoglobin Mixtures, Nature **185:** 547, 1960.
4. Robinson, E., et al.: Identification of the Recombinant Product of Canine and Human Hemoglobins, Nature **188:** 798, 1960.
5. Meyering, C. A., et al.: Studies on the Heterogeneity of Hemoglobin. II. The Heterogeneity of Different Human Hemoglobin Types in Carboxymethylcellulose and in Amberlite IRC-50 Chromatography: Quantitative Aspects, Clin. chim. acta **5:** 208, 1960.
6. Allen, D. W., Wyman, J., and Smith, G. A.: The Oxygen Equilibrium of Fetal and Adult Human Hemoglobin, J. Biol. Chem. **203:** 81, 1953.
7. Rhinesmith, H. S., Schroeder, W. A., and Pauling, L.: The N-Terminal Amino-Acid Residues of Normal Adult Human Hemoglobin: A Quantitative Study of Certain Aspects of Sanger's DNP-Method, J. Am. Chem. Doc. **79:** 609, 1957.
8. Ingram, V. M.: A Specific Chemical Difference Between the Globins of Normal Human and Sickle-Cell Anaemia Haemoglobin, Nature **178:** 792, 1956.
9. Hunt, J. A.: Identity of the Chains of Adult and Fetal Human Hemoglobins, Nature **183:** 1373, 1959.
10. Muller, C. J., and Jonxis, J. H. P.: Identity of Hemoglobin $A_2$, Nature **188:** 949, 1960.
11. Meyering, C. A., et al.: Studies on the Heterogeneity of Hemoglobin. II. The Heterogeneity of Different Human Hemoglobin Types in Carboxymethylcellulose and in Amberlite IRC-50 Chromatography: Qualitative Aspects, Clin. chim. acta **5:** 208, 1960.
12. Muller, C. J.: A Comparative Study on the Structure of Mammalian and Avian Haemoglobins, Thesis, University Groningen, Assen, Netherlands, 1961.
13. Halbrecht, J., and Klibanski, Ch.: Identification of a New Normal Embryonic Haemoglobin, Nature **178:** 794, 1956.
14. Drescher, H., and Künzer, W.: Der Blutfarbstof des menschliche Feten, Klin. Wchnschr. **32:** 92, 1954.
15. Butler, E. A., et al.: Hemoglobin of Fetal Blood, Clin. chim. acta **5:** 571, 1960.
16. Huelms, E. R., Flynn, F. V., Butler, E. A., and Beaven, C. H.: Two New Hemoglobin

Variants in a Very Young Human Embryo, Nature **189:** 496, 1961.
17. Kleihauser, et al.: Demonstration vom fetalen Hämoglobin in den Erythrozyten eines Blutausstrichs, Klin. Wchnschr. **35:** 637, 1957.
18. Ingram, V. M.: Chemistry of the Abnormal Human Haemoglobins, Brit. M. Bull. **15:** 27, 1959.
18a. Raper, A. B., et al.: Four Hemoglobins in One Individual; a Study of the Genetic Interaction of Hb-G and Hb-C, Brit. M. J. 1257, 1960.
19. Baglioni, G., and Ingram, V. M.: Genetic Control of Foetal and Adult Human Hemoglobin, Nature **189:** 467, 1961.
20. Vella, F., Ager, J. A. M., and Lehmann, H.: Haematology and Blood Transfusion Service, **183:** 31, 1959.
21. Fessas, P. H., and Paraspyrou, A.: New "Fast" Hemoglobin Associated With Thalassemia, Science **126:** 1119, 1957.
22. Rigas, D. A., Koler, R. D., and Osgood, R. E.: New Hemoglobin Possessing a Higher Electrophoretic Mobility Than Normal Adult Hemoglobin, Science **121:** 372, 1955.
23. Ager, J. A. M., and Lehmann, H.: Observations on Some "Fast" Hemoglobins: K, J, and Barth's, Brit. M. J. **1:** 929, 1959.
24. Huisman, T. H. J.: Genetic Aspects of Two Different Minor Haemoglobin Components Formed in Cord Blood Samples of Negro Babies, Nature **188:** 589, 1960.
25. Edington, G. M., and Lehmann, H.: The Distribution of Haemoglobin C in West Africa, Man **56:** 56, 1956.
26. Jonxis, J. H. P., and Delafresnaye, J. F.: Symposium on Abnormal Haemoglobins, Oxford, 1959, Blackwell Scientific Publications, p. 300.
27. Ingram, V. M.: in Sutton, Macy, and Heldon, editors: Genetic Transactions of the First Conference 1959, Josiah Macy, Jr. Foundation, 1960, p. 65.
28. Gerald, P. S., and Diamond, L. K.: The Diagnosis of Thalassemia Trait by Starch-Block Electrophoresis of the Hemoglobin, Blood **13:** 61, 1958.
29. Neeb, H., et al.: Homozygous Lepore Hemoglobin Disease Appearing as Thalassemia Major in Two Papuan Siblings, Nederl. tijdschr. geneesk. **105:** 8, 1961.
30. Gerald, P. S., and Diamond, L. K.: A New Hereditary Hemoglobinopathy (the Lepore Trait) and Its Interaction With Thalassemia Trait, Blood **13:** 835, 1958.

# CLINICAL PATHOLOGICAL CONFERENCE

## THE CHILDREN'S HOSPITAL MEDICAL CENTER

## BOSTON, MASSACHUSETTS

*Sidney Farber, M.D., Editor*

*Gordon F. Vawter, M.D., Assistant Editor*

THIS 11½-year-old white male was referred by his physician for evaluation of thyroid function. It was difficult to determine the time of onset of the boy's presenting complaints since they overlapped significantly with family problems dating back to his birth. His mother, who had majored in psychology in college, had always sought much psychological and psychiatric help, and the family had been followed by psychiatrists and psychiatric social workers for many years through a local child guidance clinic. When the child was about 3 years old, there was considerable trouble with temper tantrums and profound rages, resulting in a strong reaction of hostility on the part of his mother. With psychiatric help to mother and child, the problem was somewhat resolved by sending the patient to a nursery school. He subsequently developed fairly well, although he remained very "sensitive" and had frequent bouts of crying and "unexplained" and uncontrolled rages. Despite these behavioral problems, he scored in the superior range on intelligence tests and had done well in school.

Approximately 6 to 8 months before admission, tantrums seemed to increase in frequency and he seemed to be more restless. With this change, he had difficulty in getting to sleep. In addition, there was a definite increase in his appetite which was accompanied, however, by an appropriate weight gain. During the summer in Florida with his grandmother she commented on his "nervousness" and felt his eyes were more prominent. However, when he returned in the fall, he seemed to be his usual self.

In the course of a routine examination for school in late September (3 months before hospitalization) the above symptoms were mentioned to his physician and on examination the thyroid was palpable. For this reason, the following laboratory tests were done at that time: total iodine, 7.2 μg per cent; protein bound iodine, 5.3 μg per cent; basal metabolic rate, minus 3. Because of the enlarged gland and normal tests he was referred later for further evaluation.

In addition to his behavioral problems mentioned previously, the patient had had hay fever and asthma with repeated respira-

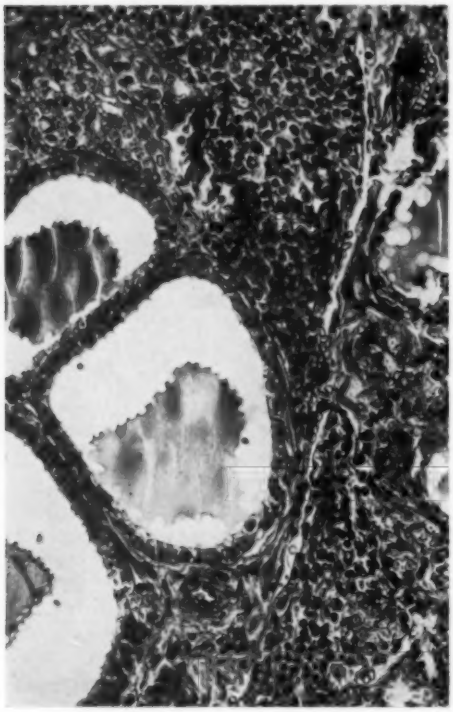


**Fig. 1.** *A.* Interstitial lymphocytic infiltrate. (Toluidine blue-eosin stain; ×175.)

tory infections from about 3 years of age. At 5 and 8 years of age, respectively, he was hospitalized for tonsillectomy and since the age of 8 had been followed by an allergist for his respiratory problems, with considerable improvement in symptoms. Otherwise past history was not contributory.

The family history is interesting in that the maternal grandmother, mother, and younger sibling had been under psychiatric care, the younger brother described as being "famous for hyperactivity." In addition, a paternal grandmother has been hospitalized at the McLean Hospital for some years for a psychiatric disorder. There was no definite family history of any thyroid disorder or of diabetes.

On examination, the patient was a moderately well-developed and nourished boy of 11½ years whose height was 59 inches (70 per cent) and weight 77½ pounds (50 per cent), who did not appear ill. He was very cooperative and not particularly overactive. The eyes were slightly prominent, the right palpebral fissure being greater than the left although there was no lid lag or weakness of convergence. The thyroid was approximately twice normal size, the lateral lobes measuring approximately 1¼ by ¾ inches. It was quite firm throughout without nodules. There was no bruit. General examination was not remarkable. The skin was normal in texture and temperature. The pulse was 64 per minute, and the blood pressure was 100/60 mm. Hg. There were no tremors or evidences of muscular weakness.

The following additional studies were made after which surgical consultation was obtained and an operation performed: Butanol extractable iodine was 5.2 μg per cent. Thyroid scan followed a 24 hour thyroidal $I^{131}$ (radioactive iodide) uptake of 34 per cent and revealed only the presence of diffuse thyroid enlargement. The basal metabolic rate was plus 8. Serum antithyroglobulin agglutination was positive at 1:320 dilution.

DR. MILTON W. HAMOLSKY.* Our problem today relates to an asymptomatic enlargement of the thyroid in an otherwise fairly healthy young male. The entire first paragraph relates to a good deal of psychological or psychiatric stress in the background. If hyperthyroidism were clear-cut, we might find ourselves criticizing these interpretations. It is often easier to obtain the past history of psychiatric distress than it is to define its precise relationship to thyroid hyperfunction. Most workers in the thyroid field think that in patients known to be hyperthyroid there is a very high incidence of prolonged or severe or sudden psychiatric stress in the background. The link between that and pathogenesis simply is unknown. In any event, about 6 to 8 months before admission there seemed to be an increase in his tantrums, increased restlessness, difficulty

*Dr. M. W. Hamolsky is Assistant Professor of Medicine and Tutor in Medical Science at the Harvard Medical School and Associate Visiting Physician and Head of Endocrine Clinic at the Beth Israel Hospital.

in getting to sleep, and a definite increase in appetite, which, however, was balanced by a gain in weight. These are the kind of symptoms that one would see in hyperthyroidism. We have had several patients in whom hyperthyroidism has clearly been associated with gain in weight. This probably relates to the balance of what "goes in" and what is "burned," and if the patient is able to eat more than his metabolism is burning up, he will gain weight. Therefore, the lack of weight loss does not rule out hyperthyroidism. One may say, if one wishes, that this represents a transient episode of hypermetabolism. Because of the symptoms and palpable thyroid, laboratory tests were performed. The results were within normal range. The frequency of upper respiratory infections in the past may be pertinent. To this audience it is a common story. We find it of significance in the history preceding thyroid enlargement in many adults, as a clue to thyroiditis. The family history recalls overactivity (psychiatric background again). I was impressed by that word, "hyperactivity," until last evening when I played with my 8-year-old son. I think I am prepared to match him with this statement.

In any event, there was no hyperactivity when the patient was admitted. As regards the asymmetry in palpebral fissures, exophthalmometric readings are more precise and help to distinguish a slight lid lag from true exophthalmos. Highly pertinent additional laboratory data indicate that a test for serum thyroid antibodies by the hemagglutination technique in this patient revealed positive results at a dilution of 1:320.

Currently we consider thyroid function as a sequence of multiple functions, rather than one specific over-all metabolic level. A special function of the thyroid is the concentration of iodide ion which, in a series of enzymatic reactions, is converted to a hypothetical iodine which then reacts with tyrosine, within the framework of the thyroglobulin molecule, to produce monoiodotyrosine and then diiodotyrosine. It is assumed that in some manner these latter substances couple and form the active hormone, thyroxin. More recently discovered is the compound triiodothyronine, which is similar to, though more potent physiologically than, thyroxin. This material is stored in the colloid of the follicle and released under the effect of a proteolytic enzyme to circulate in the plasma, bound to one or more highly specific trace proteins. By some as yet unknown mechanisms, the material enters the tissue and there exerts its calorigenic effect. Many of these steps occur autonomously in thyroid sections in the test tube, but the yields are very small and the rate slow. Thyroid-stimulating hormones from the pituitary do increase each of these steps. There is a homeostatic mechanism whereby, if the level of circulating hormone increases, the thyroid-stimulating hormone is shut off and the thyroid becomes quiescent.

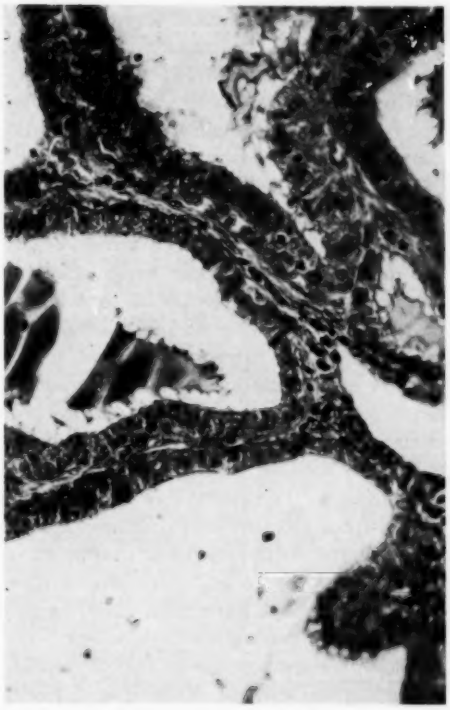


**Fig. 1.** *B.* High-power view of *A* demonstrates the tall, closely packed, hyperplastic epithelium of the thyroid. (Toluidine blue-eosin stain; ×300.)

Turning to the enlarged thyroid gland in this age group, the probabilities include: malignancy of the thyroid; thyroiditis; hyperthyroidism; the hypothyroid goiters; exposure to exogenous goitrogen; and a rather "wastebasket" term—"adolescent goiter," which is slowly being separated into various diverse conditions. The latter term simply means an enlarged thyroid in a child of this age group with no obvious explanation. As progress is made in studies of thyroid disease, there will be less and less justification for this type of category. Inherent in the term is an assumption that during adolescence there is an increased demand for hormones and in some way the body responds to this by making a bigger gland to meet the challenge. The concept is vague enough to obscure a more specific diagnosis. It may be of interest to this audience that many of the advances in the understanding of these particular diseases have been made largely in the field of pediatric endocrinology.[1] The problems concern coexistent hypothyroidism and goiter. In essence, if there is difficulty with the production of the normal thyroid hormone at any stage in the sequence, the tissues are deprived of the needed amount of hormone and the pituitary is stimulated to release TSH (thyroid-stimulating hormone) which, in turn, stimulates the thyroid to greater and greater enlargement. The propylthiouracil drugs are goitrogens because they inhibit the synthesis of normal hormones. The pituitary is fooled into believing that there is not enough, it stimulates the thyroid to make more, but the thyroid cannot because it is blocked. So one has a progressively enlarging gland. There have been many examples of this, most classically in cretins, so I think that this again is not pertinent here, but in each category of a deficiency there have been one or two essentially normal individuals (often siblings of cretins) in whom the stimulus has been enough, and the capacity to meet it just about enough, to render the patient essentially euthyroid but at the cost of a progressively enlarging, harder-working gland. For example, just yesterday, Dr. Stanbury presented the case of a hypothyroid individual in whom there had been impaired ability to transmit iodide from the serum to the thyroid. As a result, the iodide could not be concentrated, hormones were not synthesized, and the patient was a hypothyroid individual with a progressively enlarging thyroid gland. There are several cretins who take up plenty of iodine but who, possibly through some inborn metabolic defect, cannot take the iodide to monoiodotyrosine and diiodotyrosine. There are cretins who cannot couple iodinated tyrosines to form normal thyroid hormone. There are still others who go through various steps in hormone synthesis and then make some sort of material which comes out in the circulation bound to protein, and yet they are cretins. It is possible, therefore, to have a cretin who has a high $I^{131}$ uptake and a high protein-bound iodine level, which suggests thyrotoxicosis but is not, because the same ultimate lack of normal thyroid hormone obtains. In families with these various defects, there may be one or two siblings who have just enough capability to increase thyroid mass to keep from becoming frankly hypothyroid unless some unusual stress is presented to them, when the compensation may fail. In such instances, the pathologist describes gross hyperplasia. These individuals usually have a high $I^{131}$ uptake. Some of them will have a prompt drop in thyroid $I^{131}$ content when given thiocyanate after the tracer which replaces the iodide. In the normal individual, the iodine which is rapidly incorporated into organic compounds is not dischargeable by thiocyanate.

Now, we return to the patient under discussion. We cannot, on the basis of the laboratory data, support the diagnosis of hyperthyroidism, as we might if one of his laboratory tests were out of line. The sum total of calorigenic effects on tissue, the basal metabolic rate, is normal. The protein-bound iodine, representing the balance between the amount of iodinated compound introduced into and removed from the circulation as bound to protein, is essentially at the normal of 4 to 8 $\mu$g per cent, of which 1 to 1.5 $\mu$g

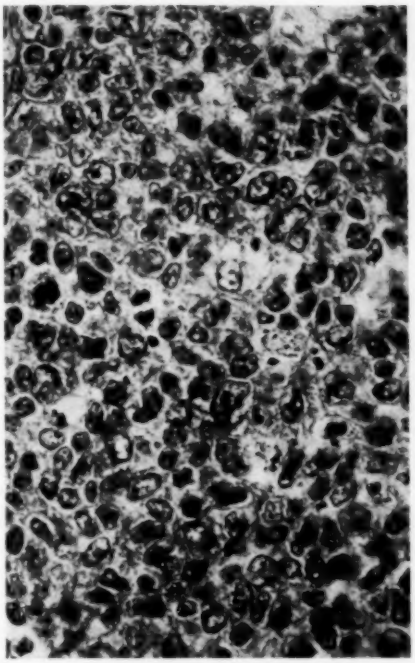


**Fig. 2.** High-power view of proliferating lymphoid germinal center found in several areas of the lymphoid infiltration of the thyroid gland. (Toluidine blue-eosin stain; ×305.)

represent iodide. Since some of the compounds artificially contributing to the protein-bound iodine level are not soluble in butanol, as are thyroxin and triiodothyronine, we are interested in the normal butanol extractable iodine. For example, some of the cretins who make abnormal iodinated protein would have a low butanol extractable iodine but a normal or high protein-bound iodine level. The uptake of $I^{131}$ is likewise a balance between the amount taken into the gland and the amount already processed through the gland. Our patient has an uptake of 34 per cent, in the normal range of 20 to 40 per cent.

There is no history of ingestion of goitrogens, such as may be demonstrated experimentally in animals fed turnips and certain fruits. It is assumed that such agents may act by preventing iodination of organic compounds, as occurs with the use of propylthiouracil. Under such circumstances the $I^{131}$ uptake would be low.

The lack of comment on fixation of gland, the absence of enlargement of lymph nodes, and the rather soft, diffuse character of the gland do not suggest the presence of cancer but, to be certain, one would be forced to do a biopsy for histologic diagnosis.

In essence, I think our problem in this instance resolves into a choice between adolescent goiter, whatever that may be, and thyroiditis. One would like to highlight the problem of thyroiditis, which often has the earmarks of an autoimmune disease, as defined by Dr. Klemperer. Historically, this concept began when Dr. Witebsky ground up one half of the thyroid of a rabbit, injected the material into another rabbit, or even back into the same animal, only to find specific histologic changes developing in thyroid, quite comparable to those seen in thyroiditis or in Hashimoto's struma.[2] Other investigators in England then looked for antibodies in the serum of human patients with thyroiditis. The fact now emerges that thyroglobulin of the follicle does not normally enter the tissues and, when it does so, it is treated as a foreign protein. Antibody to thyroglobulin is formed, leading (according to one present concept) to tissue damage in the thyroid and thus the cycle repeats itself.

To begin the process we might assume an infection of the thyroid, and we recall the apparent relation of upper respiratory infection to thyroid disease. Many times, in our cases of clinical thyroiditis, we get the story of a very bad sore throat, peculiar in that the patient's collar became too tight and there was tenderness superficially in the neck. A fairly clear definition of such a possible relationship was described in Israel when an epidemic of thyroiditis followed an epidemic of mumps. Indeed, in 2 of these patients with thyroiditis, mumps virus was cultured from the thyroid gland. Strong agglutinating antibody titers against mumps virus were demonstrated in the patients with thyroditis in Israel, and subsequently in England.

However, the problem is not that simple,

since at present there are considered to be three groups of antigens in thyroid tissue. Antibody to a microsomal fraction of thyroid gland seems to have stronger effects upon thyroid tissue than does antithyroglobulin; both may be implicated in disease in varying circumstances. Recently, an apparently distinct material has been found in serum of certain patients, usually with clinical thyroiditis, which is, in very small doses, rapidly and specifically cytotoxic to human thyroid gland growing in tissue culture. This substance is nondialyzable and is heat stable, requires complement for activity, and has been found in Cohn's fractions II and III of plasma protein.

The picture becomes more complicated when we recognize that 60 to 70 per cent of adult patients with myxedema have positive antithyroid agglutination and precipitin tests. Often the pathologists will tell us that the thyroid of such patients resembles a burned-out thyroiditis. Therefore, we cannot use these tests to predict active thyroiditis. Second, these tests are positive in about 80 per cent of thyrotoxic patients. This raises all sorts of questions which cannot be answered as yet. However, malignancy does not in itself produce these phenomena, but again the positive test does not exclude the coexistence of thyroiditis and cancer, while a repeatedly negative result would be worrisome indeed. Usually, of course, the episode of thyroiditis subsides in 3 to 5 weeks but some have progressed to the unusual sequel of hypothyroidism.

We have seen one patient who seemed to start out with mild thyroiditis with an acute but mild episode suggesting thyrotoxicosis, perhaps following release of excess thyroxin by the inflammatory process, in whom the ultimate progress was to that of full-blown persisting thyrotoxicosis.

We may well wonder if the patient discussed today might not some day fall into this pattern. After all, what really did happen to him during that ill-defined episode 6 to 8 months prior to admission? Might he not have had mild thyroiditis and thyrotoxicosis at that time? It is hard to ignore the antithyroglobulin agglutination titer of 1:320 which was found in this patient.

Dr. C. D. Cook has just shown me a report from another hospital of the high incidence of high agglutination titers in a group of patients studied for adolescent goiter. We have recently learned that there is an appreciable incidence of elevated antithyroglobulin agglutination titers in the asymptomatic members of the families of patients with proved thyroiditis.

In summary, I think the patient may have had thyroditis 6 to 8 months previously, and that at the time of operation he was euthyroid.

Dr. Sidney Farber. Does anyone else want to offer a diagnosis?

Dr. David H. Carver. The third year students diagnosed adolescent goiter; the fourth year students, thyroiditis with psychosomatic overlay; the junior and senior house officers diagnosed nontoxic diffuse goiter.

Dr. Don Singer. Surgical biopsies were taken from each lobe and from the isthmus of the thyroid. These biopsies all contain relatively large amounts of lymphoid tissue with active germinal centers, changes consistent with *Hashimoto's disease* (Fig. 1). In the rest of the gland there are changes suggesting *hyperplasia* (Fig. 2) and thyroid hyperactivity, which raise the issue of thyrotoxicosis. These changes include: the controversial retraction vacuoles in the margin of the colloid, increase in height, and close packing of acinar cells with actual papillary budding of the epithelium into the follicles. These changes differ somewhat from the hypertrophy and giant cell formation of thyroid epithelial cells described in Hashimoto's disease.

Dr. John F. Crigler. Can we really tell whether this is hyperplasia, as distinct from thyroiditis?

Dr. Gordon F. Vawter. I believe the epithelial changes are those of hyperplasia, and do not actually resemble the hypertrophy, rather than hyperplasia described by Dr. Hashimoto. Noteworthy too, perhaps, is the lack of scarring. Plasma cells and eosinophils, prominent in some instances of

thyroiditis, were not identified. However, just because these areas are hyperplastic, it is not necessarily true that enough of the whole gland will be similarly involved and thereby give measurable functional changes.

DR. CRIGLER. I would expect to see hyperplasia resulting from the same mechanisms which produce the hypertrophy in chronic thyroiditis. In other words, these areas, local though they may be, may reflect the same abnormality that induces the lymphoid infiltration.

We have followed the patient since operation. Two months afterward our tests indicated that he was still euthyroid. However, 10 months postoperatively, the butanol extractable iodine became elevated, suggesting that thyrotoxicosis was present, though his pulse rate did not exceed 80 and there was not any other cardiac manifestation of the hyperthyroid state. A little tremor became apparent. Later on, I though that the goiter had increased still further, and at this time the basal metabolic rate was elevated. Finally, we attempted to suppress the $I^{131}$ uptake with thyroxin as should occur in the normal individual or the individual with thyroiditis, when some of the stimulation presumably comes from pituitary thyroid-stimulating hormone. However, the $I^{131}$ uptake remained elevated, despite administration of thyroxin, as will occur in thyrotoxicosis. We might well have used this test earlier to advantage in assessment of his condition.

DR. FARBER. Do you feel that this sort of response would exclude malignancy?

DR. CRIGLER. Cancer and thyroxicosis have only very rarely coexisted.

DR. HAMOLSKY. I am not sure that early in his course one would have been able to demonstrate evidence of hyperfunction by this test.

DR. CRIGLER. It all comes down to the fact that we do not know the etiology of hyperthyroidism with its unexplained exacerbations and remissions.

## REFERENCES

1. Stanbury, John B., Wyngaarden, J. B., and Fredrickson, D. S.: The Metabolic Basis of Inherited Disease, New York, 1960, McGraw-Hill Book Company, Inc., chap. 9.
2. Paterson, Philip Y.: Thyroiditis, in Lawrence, H. Sherwood, editor: Cellular and Humoral Aspects of the Hypersensitive States, New York, 1959, Hoeber-Harper, pp. 490-495.

# COMMENTS ON CURRENT LITERATURE

## *Latent virus infection: recurrent herpes simplex*

HERPES SIMPLEX is one of the most widespread viral infections of man; it results in a variety of clinical entities, some of which have been recognized only within recent years. It is also one of the few viral agents that remain latent in human tissues, including nerve tissue, for a prolonged period. Infants born of immune mothers show circulating antibodies for about the first 6 months of life, an observation which may account for the rarity of herpetic infection in infants under 6 months of age. However, infection does occur in the newborn infant, producing a disseminated, often fulminating systemic disease with hepatitis; in nearly every instance such infections are associated with known herpetic infection in the mother. This fatal disease in the newborn infant can occur in the absence of significant skin lesions. Susceptibility is high in infancy and childhood after the age of 6 months, and decreases with age.

In general, primary infection takes the form of a gingivostomatitis which varies individually in degree and extent, followed by a latent infection persisting throughout life. The latent virus may be activated by various physiologic states, emotional stress, malnutrition, irritation or trauma, or the occurrence of bacterial or other infections in the body. The host-parasite relationship has been charted in detail by Blank and Rake[1] who state that in about 99 per cent of the primary exposures the infection is subclinical, and that in about 1 per cent primary exposure results in clinical disease, both giving rise to a carrier state (70 to 90 per cent of the population) with persistent antibodies. Recurrent clinical episodes in latent carriers complete the cycle to new susceptible hosts. While primary infection may occur in the older child or later in life in the form of encephalitis, this type of invasion is relatively uncommon in the human subject, despite the widespread incidence of herpetic infections. In experimental animals, however, strains of herpes simplex virus show marked neurotropism. In human subjects a number of fatal cases has been reported in which strains of this virus were isolated from tissue of the brain, showing pathologic changes characteristic of encephalitis and intranuclear inclusion bodies of the herpetic type. The virus has been isolated also from blood, spinal fluid, feces, cutaneous lesions, lesions of the mucous membranes, etc.

A common recurrent form of the infection consists of vesicular lesions of the lips, and the virus is thought to be latent in the epithelial cells of the upper respiratory tract and of the mouth. The presence of antibody does not appear to prevent superficial recurrences. Recurrent herpetic lesions may occur also on the genitals and on the cornea,

both of which may be extremely painful and troublesome. In some patients, particularly those with lesions of the thigh and inguinal region, the lesions may be "zosteriform" in character following a nerve distribution and may be associated with regional adenopathy and vague deep-seated pain. Recurrent herpetic infection commonly affects the eye, producing keratitis or keratoconjunctivitis. Thygeson[2] has considered this the most important specific form of keratitis occurring in the United States in recent years. On occasion recurrent herpes simplex infections have been a problem following surgical section of nerves performed for the relief of pain. Following preganglionic section of the trigeminal nerve performed for the relief of trigeminal neuralgia, herpetic eruptions frequently appear which involve the denervated surface area.[3] Repeated infection with herpes virus is also possible in patients with eczema, neurodermatitis, and other chronic skin irritation, resulting in disseminated cutaneous herpes or eczema herpeticum.

During the past few years various studies in experimental animals have been undertaken in an attempt to understand the pathogenesis of latent infection with herpes virus and the recurrent clinical manifestations in the human subject. One of the earliest reports dealing with induced reactivation of herpes infection in an experimental animal was that of Good and Campbell[4] who found anaphylactic and histamine shock effective in potentiating herpetic encephalitis in rabbits previously inoculated with virus. Subsequent investigations by these authors concerned with induced encephalitis in rabbits included recovery and identification of the virus.[5] More recently Schmidt and Rasmussen[6] reported the stress activation of latent encephalitis by chemical means, specifically the use of repeated intramuscular injections of epinephrine. Two publications appearing recently in the *Proceedings of the Society for Experimental Biology and Medicine* are of interest. One of these reports is by Anderson, Margruder, and Kilbourne,[7] and deals with a study of induced reactivation of herpes virus in healed corneal lesions in rabbits. Reactivation was brought about by induction and evocation of local hypersensitivity reactions of the Arthrus type. Initial infection of the cornea was accomplished by dropping virus suspension into the eye with or without corneal scarification. Within a period of 2 to 4 days mucopurulent exudate, chemosis, and photophobia were noted. The acute inflammation subsided and epithelial repair was completed within about 14 days, leaving residual scarring in most instances. Exudate collected during the acute phase yielded virus by tissue culture which appeared to be completely identical with the original strain. Six to 9 weeks after corneal infection the animals were sensitized to horse serum and an Arthrus reaction was induced in the healed cornea. Herpes virus could be recovered with regularity following such stress phenomena. The authors were impressed by the ease with which virus recovery could be accompilshed at widely spaced intervals and after long periods of quiescence. They conclude that such herpes simplex infection of the cornea in the rabbit "closely parallels the syndrome of recurrent human cutaneous, ocular, mucous membrane herpes simplex infection and affords an accessible model for experimental study."[7]

The other publication which appears in the same issue is by Anderson and Kilbourne.[8] This report concerns the immunization of mice, an extremely susceptible host, against strains of herpes simplex virus in an attempt to understand the immunogenic characteristics of this "prototype of mammalian virus latency." Mice were immunized by ultraviolet-inactivated herpes virus suspensions prepared from rabbit kidney cell cultures. Immunization was carried out by intravenous and intraperitoneal inoculation. Demonstrable levels of neutralizing antibody were comparatively high following immunization, and the mice so protected by antibody were able to withstand subsequent challenge doses of live virus by intracerebral inoculation. Latency of herpes virus infection studied in such immunized animals will be of considerable

practical interest. In both these reports the results are preliminary, and the investigations are being continued.

Experimental studies such as these may lead to a better understanding of latent virus infections in general and might throw some light on the phenomenon of recrudescence in the human subject.

RUSSELL J. BLATTNER, M.D.

## REFERENCES

1. Blank, Harvey, and Rake, Geoffrey: Herpes simplex, in Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man, Boston, 1955, Little, Brown & Company, chap. 3, p. 43.
2. Thygeson, P.: Herpes Corneae: An Editorial, Am. J. Ophth. **36:** 269, 1953.
3. Ellison, S. A., Carton, C. A., and Rose, H. M.: Studies on Recurrent Herpes Simplex Infections Following Section of the Trigeminal Nerve, J. Infect. Dis. **105:** 161, 1959.
4. Good, R. A., and Campbell, Berry: Potentiating Effect of Anaphylactic and Histamine Shock Upon Herpes Simplex Virus Infection in Rabbits, Proc. Soc. Exper. Biol. & Med. **59:** 305, 1945.
5. Good, R. A.: Recovery of Herpes Simplex Virus From Rabbit Brain Nine Months After Inoculation, Proc. Soc. Exper. Biol. & Med. **64:** 360, 1947.
   Good, R. A., and Campbell, Berry: The Precipitation of Latent Herpes Simplex Encephalitis by Anaphylactic Shock, Proc. Soc. Exper. Biol. & Med. **68:** 82, 1948.
6. Schmidt, J. R., and Rasmussen, A. F., Jr.: Activation of Latent Herpes Simplex Encephalitis by Chemical Means, J. Infect. Dis. **106:** 154, 1960.
7. Anderson, W. A., Margruder, B., and Kilbourne, E. D.: Induced Reactivation of Herpes Simplex Virus in Healed Rabbit Corneal Lesions, Proc. Soc. Exper. Biol. & Med. **107:** 628, 1961.
8. Anderson, W. A., and Kilbourne, E. D.: Immunization of Mice With Inactivated Herpes Simplex Virus, Proc. Soc. Exper. Biol. & Med. **107:** 518, 1961.

# Books

## New books received

Selected books will be reviewed in subsequent issues.

**Cancer in Childhood and Youth.**
Sigismund Peller, M.D., F.RS.H., Bristol, England, 1960, John Wright & Sons, Ltd. (in U.S., Williams & Wilkins Company, Baltimore), 291 pages. Price $8.75.

**Chemicals in Your Food and in Farm Produce: Their Harmful Effects.**
Franklin Bicknell, New York, 1961, Emerson Books, Inc., 192 pages. Price $2.95.

**Ciba Foundation Symposium on Quinones in Electron Transport.**
Boston, 1961, Little, Brown, & Company, 453 pages. Price $11.00.

**Congenital Anomalies of the Face and Associated Structures.**
Proceedings of an International Symposium, Springfield, Ill., 1961, Charles C Thomas, Publisher, 385 pages. Price $13.25.

**Diabetes Infantil.**
Horacio I. Burgos, Buenos Aires, 1961, Editorial Vergara, 159 pages. Price 380 pesos.

**The Electroencephalogram of the Normal Child.**
Alberto Fois, M.D., translated and edited by Niels L. Low, M.D., F.A.A.P., with prefaces by Professor Dr. Angelo Chieffi and Frederic A. Gibbs, M.D., Springfield, Ill., 1961, Charles C Thomas, Publisher, 124 pages. Price $6.75.

**Foetal and Neonatal Physiology.**
British Medical Bulletin, Volume 16, Number 2, London, England, 1961, Medical Department, The British Council. Price $3.25.

**The Gustav Stern Symposium on Perspectives in Virology.**
Morris Pollard, editor, Volume 2, Minneapolis, 1961, Burgess Publishing Co., 220 pages. Price $8.00.

**Human Psychological Development.**
Elizabeth Lee Vincent and Phyllis C. Martin, illustrated by William A. Osborn, New York, 1961, The Ronald Press Co., 522 pages. Price $6.50.

**Manual of Pediatric Physical Diagnosis.**
Lewis A. Barness, M.D., edition 2, Chicago, 1961, Year Book Publishers, Inc., 208 pages. Price $4.00.

**Mental Health in the United States; a Fifty-Year History.**
Nina Ridenour, Ph.D., Cambridge, 1961, Commonwealth Fund, Harvard University Press, 146 pages. Price $3.50.

**Mikromethoden für das klinisch-chemische und biochemische Laboratorium.**
Hermann Mattenheimer, Berlin, 1961, W. de Gruyter, 146 pages. Price 16 DM.

**Onsets, Completions, and Spans of the Osseous Stage of Development in Representative Bone Growth Centers of the Extremities.**
S. Idell Pyle, Harold C. Stuart, Joan Cornoni, Robert B. Reed, Lafayette, Ind., Purdue University.

**Child Development Publications of the Society for Research in Child Development, 1961,** 126 p. $3.25. Monographs of the Society for Research in Child Development, Serial No. 79, Volume 26, No. 1, Longitudinal Studies of Child Health and Development, Series II, No. 12, Harvard School of Public Health, 126 pages. Price $3.25.

**Pädopathologie; Kyematopathien, Neogonopathien; Thelamonopathien.**
Leipzig, 1961, George Thieme Verlag, 522 pages. DM 138.

**Parental Attitudes and Child Behavior.**
John C. Glidewell, Ph.D., editor, David J. Pittman, Ph.D., James M. Vanderplas, Ph.D., Albert F. Wessen, Ph.D., George Winokur, M.D. With a foreword by Raymond Fledman, M.D. Springfield, Ill., 1961, Charles C Thomas, Publisher, 253 pages. Price $8.50.

**Peter and Caroline: A Child Asks About Childbirth and Sex.**
Translated from the Danish. With introductory comments by Alexandra Adler, M.D., and W. C. W. Nixon, M.D., drawings by

Gerda Nystad, London, New York, 1961, Abelard-Schuman, Ltd., 34 pages. Price $2.00.

**The Premature Baby.**
V. Mary Crosse, edition 5, Boston, 1961, Little, Brown & Company, 266 pages. Price $7.00.

**Reading, Writing and Speech Problems in Children; a Presentation of Certain Types of Disorders in the Development of the Language Faculty.**
Samuel Torrey Orton, M.D., first published in 1937. New York, 1961, W. W. Norton & Company, Inc., 215 pages. Price $4.95. (Books that live in psychiatry.)

**Röntgenatlas der entzündlichen Lungenerkrankungen und ihrer Differentialdiagnose im Kindesalter.**
Leipzig, 1961, George Thieme Verlag, 270 pages. DM 41.30.

**Speech and Hearing Problems; a Guide for Teachers and Parents.**
Charles E. Palmer, Ph.D., with a foreword by John W. Kidd, Springfield, Ill., 1961, Charles C Thomas, Publisher, 137 pages. Price $5.50.

**Virus Meningo-Encephalitis.**
Wolstenholme, G. E., and Cameron, Margaret P., editors, Ciba Foundation Study Group No. 7, in honour of Professor K. Todorovic, with 11 illustrations, Boston, 1961, Little, Brown & Co.

**You and Your Doctor; the Common-Sense Guide to Medical Care.**
New York, 1961, Duell, Sloan, & Pearce, Inc., 288 pages. Price $3.00.

# Correspondence

## Sagittal synostosis: indications for operation

*To the Editor:*

The recent paper entitled "Craniosynostosis involving the sagittal suture only: Guilt by association?" by Hemple, Harris, Svien, and Holman (J. PEDIAT. 58: 342, 1961) raises certain questions regarding the advisability of surgical therapy in premature closure of the sagittal suture. Our opinion on this matter has been sought and is, therefore, stated here briefly. This opinion is based on 394 operations for craniosynostosis which have been performed at the Children's Hospital Medical Center in Boston, 207 of which were for isolated sagittal synostosis.

There are 2 reasons for carrying out operative treatment of craniosynostosis; first, a cosmetic deformity can be lessened or completely alleviated, and, second, impairment of function which may result from constriction or distortion of the growing brain can be minimized. The extent of neurological deficit varies with the number of sutures involved. At the 2 extremes, prognosis is reasonably clear. In a child with synostosis of all the major cranial sutures (sagittal, coronals, lambdoids, and squamosals), the restricting effect on the growth of the brain is maximal, and increased intracranial pressure is present at birth. On the other hand, it is highly questionable whether synostosis of one lambdoid suture alone, for example, can distort the brain sufficiently to produce any general or focal abnormality of the central nervous system.

In this clinic, papilledema has never been seen in any patient with untreated synostosis of the sagittal suture alone nor can any change in intelligence which unquestionably resulted from surgical correction of sagittal synostosis be documented. This is, in part, due to the fact that operations in general have been performed within the first few weeks or months of life when preoperative intelligence quotients cannot be estimated. There have been many statements from parents of improvement in behavior and of acceleration in the learning of motor and mental skills following treatment in the age group between 1 and 4 years, but such clinical impressions also are difficult to confirm. There is no doubt that multiple suture closure has been accompanied by chronically increased intracranial pressure and by marked retardation as well as by visual, auditory, and other defects. It has always seemed reasonable to us that the best way to avoid the possibility of lesser degrees of intellectual impairment which might ensue from a lesser extent of craniosynostosis would be to carry out surgical correction as early in life as possible.

The cosmetic deformity caused by sagittal synostosis may be striking, even shortly after birth. Untreated, it ordinarily increases in severity until the period of rapid brain growth ceases. There is absolutely no question that this cosmetic deformity can be greatly improved by appropriate operation. The degree of improvement varies with the age of the patient at the time of initial operation, the adequacy of operation, and the maintenance of patency of the craniectomies throughout the period of active brain growth. This improvement has been documented repeatedly with photographs and with roentgenograms, on which the increase in width of the original craniectomies can be measured.

Adequate correction of sagittal synostosis requires that the parietal bones be separated from one another completely and that this separation be maintained until the child is at least 3 years old. Surgical failures occur when the craniectomy is not carried well across the coronal and lambdoid sutures or when new bone bridges and fuses the craniectomy before 3 to 4 years of age.

The morbidity and mortality rates are low enough to justify surgical correction of sagittal synostosis in early life for cosmetic reasons alone.

There have been 2 deaths in our entire series of 394 patients. One of these was due to a hereditary coagulation defect unsuspected until the time of operation, the other due to cardiac arrest. Morbidity has been negligible.

Our current policy is to explain the mechanics of this developmental problem to parents and to recommend without qualification during the first few months of life that surgical correction of sagittal, as well as all forms of craniosynostosis, be performed for cosmetic reasons alone. Parents are then also advised that although mental retardation due to sagittal synostosis alone has not been documented, we feel it probable that optimum development and function of the brain is permitted by providing it the chance to assume its natural shape and rate of expansion as soon as possible.

JOHN SHILLITO, JR., M.D.
DONALD D. MATSON, M.D.

## Reply

*To the Editor:*

It is apparent from the comments of Drs. Shillito and Matson that they are in agreement with our opinion that patients with isolated synostosis of the sagittal suture do not develop papilledema, and that they did not document any change in intelligence that unquestionably resulted from surgical correction of sagittal synostosis.

We are glad to have them state definitely that their policy is to recommend craniectomy for cosmetic reasons alone. Their qualifying statement in regard to "optimum development and function" brings to mind the words from our paper: "In the uncertainty as to whether surgical treatment is indicated for the reasons of preventing increased intracranial pressure and allowing normal growth of the brain, many have proclaimed craniectomy desirable for the cosmetic effect."

On the basis of the extensive experience of Drs. Shillito and Matson in this problem and their statements of their indications for craniectomy in the child with isolated synostosis of the sagittal suture, the pediatrician, neurosurgeon, and parent should be able to choose surgical treatment on the basis of cosmetic effect alone. It has been unfortunate that in the absence of documented evidence parents have been advised that without surgical treatment developmental retardation would ensue.

The mortality rate cited is indeed low. It is not stated whether the 2 deaths were in infants with isolated closure of the sagittal suture or in the remainder of the group containing those with more severe forms of craniosynostosis. The question whether even this low mortality rate can be accepted for cosmetic surgical treatment becomes somewhat philosophic. It would be of assistance to those suggesting operation if the other centers would report their morbidity and mortality rates in this type of case.

LLOYD E. HARRIS, M.D.

# News and notes*

The **Nineteenth annual meeting of the American Psychosomatic Society** will be held at the Sheraton Hotel in Rochester, New York, March 30 to April 1, 1962. Abstracts of original work to be presented at the meeting by members or nonmembers of the Society, are welcomed; they should be not longer than 2 typewritten pages and should be submitted in 11 copies, before Dec. 1, 1961, to the Chairman, Stewart Wolf, M.D., 265 Nassau Road, Roosevelt, New York. The Review Committee consists of the following: Eugene L. Bliss, M.D., Hilde Bruch, M.D., W. Horsley Gantt, M.D., David T. Graham, M.D., David A. Hamburg, M.D., Lawrence S. Kubie, M.D., John W. Mason, M.D., Dane G. Prugh, M.D., and Seymour Reichlin, M.D.

Tulane University School of Medicine announces a subspecialty course for pediatricians on **Immunology and Allergy in Pediatrics** to be held from Feb. 12 to 16, 1962. Comprehensive instruction in the fundamentals of immunology will be offered. Guest speakers will be Dr. Victor Vaughan of the University of Georgia, and Dr. Harry Mueller, of Harvard.

On April 14, 1961, the **Cincinnati Pediatric Society** honored Dr. Robert A. Lyon by presenting him with a "Distinguished Service Award" which consisted of a hand-lettered certificate prepared by the Medical Arts Department of the College of Medicine and bearing the following inscription:

DISTINGUISHED SERVICE AWARD

In grateful appreciation for the many years of devotion to the children of this community, the Cincinnati Pediatric Society hereby honors

ROBERT A. LYON

for his outstanding service as teacher, counselor and friend to his students, investigator, pediatrician and civic minded citizen.

Among his many achievements are the following:

Professor of Pediatrics, College of Medicine, University of Cincinnati

Asst. Director of Pediatrics, Cincinnati General Hospital

Assoc. Chief of Staff, Children's Hospital

Asst. Medical Director, Babies' Milk Fund Association

President, Cincinnati Pediatric Society

President, Medical and Dental Staff of the Children's Hospital

Founder: Children's Heart Association and Children's Cardiac Clinics, Cincinnati General Hospital and Children's Hospital
Children's Dental Care Foundation
Child Health Association
Obstetrical Foundation
State Children's Cardiac Diagnostic Clinics
Adolescent Clinic Cincinnati General Hospital
Pediatric Care for the Newborn at General Hospital, Cincinnati

Inspiration for Improvement in the County School Health Program and the County Well Baby Clinics.

This document is presented to him on this eleventh day of April, nineteen hundred and sixty one as evidence of the esteem in which he is held by his friends, colleagues and members of the Cincinnati Pediatric Society.

*Notices of meetings must be in the hands of the Editor 3 months in advance of the date in order to appear in the JOURNAL in time.

# EDITOR'S COLUMN

## *The relationship between pediatrics and preventive medicine*

EARLY in his career, Dr. Edwin H. Schorer* realized that if preventive measures are properly performed in the antenatal, natal, and postnatal periods, most of the worst pediatric diseases could be reduced to a minimum, and the pediatrician or family physician could concentrate his efforts on maintaining child health rather than on diagnosis and treatment.

### THE EVOLUTION OF PREVENTIVE PEDIATRICS

As a result of this emphasis on preventive medicine in pediatrics, more progress has been made in the care of children during the half century since Dr. Schorer entered pediatrics and preventive medicine than in the 2,333 years since the death of Hippocrates. Until 1900, only breast-fed children of healthy stock in a good environment had much chance of survival. Just 2 diseases, smallpox and scurvy, were preventable. *Specific* drugs were available for only 3 conditions: malaria, which was usually cured by quinine; worms, which succumbed to many remedies, including garlic; and scabies, which was relieved by sulfur. In 1906 there were less than 100 pediatricians throughout the world; now there are more than 6,000 in this country alone. Pediatrics was not taught in any medical school, except for occasional references to it by obstetricians and internists.

From 1900 to the beginning of the first World War, pediatrics was largely concerned with infant feeding and the knowledge of nutrition progressed rapidly. Although Shakespeare's physician son-in-law, John Hall, used tamarind (of the bean family) in the treatment of scurvy[1] and oranges were brought to this hemisphere from Spain by Christopher Columbus, it was not until 1906 —the year Dr. Schorer was graduated from medical school—that the concept of vitamins was introduced by Sir Frederick Gowland Hopkins and Casimir Funk.[2] Nowadays pellagra, rickets, and scurvy are curiosities. The compulsory tuberculin testing of cattle and pasteurization of milk, the United States Public Health Service Milk Ordinance, and especially the simplification of infant feeding

*The Edwin Henry Schorer Lecture, given at Kansas City Southwest Pediatric Society, Kansas City, Missouri, Sept. 27, 1960.*

**The career of Dr. Edwin Henry Schorer—Teddy to his many friends—illustrates the increasing closeness of pediatrics and preventive medicine. Dr. Schorer has been and is a leader in this field of preventive pediatrics, and Kansas City and the country are fortunate to have him. Dr. Schorer was born in Plymouth, Wisconsin, on Dec. 13, 1881. He received a B.S. degree from the University of Wisconsin in 1902, and an M.D. from the Hopkins University in 1906. His pediatric training, a rarity in those days, was obtained from J. H. Mason Knox at the Thomas Wilson Sanatorium, and as a resident at the old Boston Floating Hospital. After serving as an assistant in bacteriology at the Rockefeller Institute, he taught bacteriology, pathology, and parasitology at the Universities of Missouri and Kansas. In 1912 he was graduated from Harvard in the first class to receive a degree in Public Health. During the first World War he served as Director of the Division of Laboratories and Communicable Diseases at the eastern ports of embarkation, with the rank of Lieutenant Colonel. Since 1919, he has been in the private practice of pediatrics in Kansas City, and from 1935 to 1940 he was Director of Health for Kansas City. I admire him not only for the qualifications and services just enumerated, but also because he is a lover of children and last, but not least, a devoted admirer of Osler.*

through the use of evaporated milk have now made it possible for artificially fed infants to thrive satisfactorily.

When Dr. Schorer started in practice, pediatricians were consultants and usually saw only those children referred to them by family doctors; they rarely provided routine child care, as does the practicing pediatrician in America today. It was not until after the first World War that child care and disease prevention became increasingly important in medical practice, and pediatricians became general practitioners for children. Routine immunizations reduced the incidence of diphtheria, pertussis, smallpox, tetanus, typhoid, and paratyphoid, as well as the rarer diseases of the tropics such as cholera, plague, typhus, and yellow fever. Clean milk, window screens, and DDT controlled diarrhea and dysentery. Health laws have made congenital syphilis a rarity. Malaria has ceased to be a problem except in Asia and Africa. The value of the Salk, Sabin, Cox, and Koprowsky poliomyelitis vaccines has been established, and the results of immunization against measles, mumps, and influenza are promising.[3]

## THE NEED FOR CONTINUED PROGRESS

In spite of this growing union between pediatrics and preventive medicine, there are still fertile areas for more progress as, for example, in the prevention of tuberculosis. While tuberculin tests, chest roentgenograms, case-finding programs, sanatorium care, isoniazid and other drugs have reduced the death rate from tuberculosis *after* it has been acquired, *the annual number of new tuberculous infections has been only slightly reduced in the past 30 years.* A new case occurs every 6 seconds in this country. Something more is needed to bring results comparable to those achieved in the control of diphtheria, smallpox, and typhoid; that something is BCG* vaccination. Members of the American medical profession (like some of their British and Scandinavian colleagues) should use BCG vaccine, especially for newborn infants, hospital personnel, and students of medicine and nursing.

Like any preventive or therapeutic measure, BCG carries a "calculated risk." The deaths of one adult, one 7-year-old child, and 3 infants have been attributed to BCG, and in the Lübeck disaster in 1930 there were 72 deaths among the 251 infants who were mistakenly given a vaccine made from virulent tubercle bacilli instead of the attenuated BCG vaccine. Lupus and lupomas are rare temporary complications of BCG vaccination. Since 1946, on the other hand, more than 270 million children and adults have been safely vaccinated with BCG. Furthermore, tuberculous meningitis, at present the greatest problem in tuberculosis, has been reported in only 2 infants who have been vaccinated with BCG. The fact that almost all cases of tuberculous meningitis occur before the age of 4 years emphasizes the need for the administration of BCG to newborn infants. Amazingly, however, many pediatricians and general practitioners are not even giving routine tuberculin tests to infants and children, on the ground that a positive reaction alarms the mother. Quite the reverse, a negative test should be even more alarming and should call for the protection of BCG.[4]

## THE CONTRIBUTION OF PEDIATRICIANS TO PREVENTIVE MEDICINE IN THE ARMED SERVICES

The relationship between pediatrics and preventive medicine is best illustrated by the contribution of pediatrics to the health of the Armed Services. During both World Wars communicable diseases, including those which are primarily pediatric conditions, were responsible for more days lost, more hospital admissions, and more deaths than were war injuries. In World War II, as soon as a recruit was inducted into the Armed Services, he was subjected to such screening measures as Schick, tuberculin, and Wasser-

*Bacille Calmette Guérin vaccine is made from an attenuated bovine strain of *Mycobacterium tuberculosis*, and is obtainable from the Research Foundation, 70 West Hubbard Street, Chicago 10, Ill.

mann tests, a chest x-ray, and to such protective measures as vaccinations against smallpox, typhoid and paratyphoid fever, and tetanus.

Pediatricians serving as medical officers with troops, as well as those in civilian practice, must concern themselves with the reduction of communicable diseases among adults as well as children. In peace time, pediatric officers of the Army, Navy, and Air Force are among the busiest in the medical corps, providing care for the children of dependents, operating dispensaries, enforcing the immunization program, and persuading commanding officers of military hospitals to abandon nurseries for the newborn and to use the "rooming-in plan" in order to eliminate infections with Staphylococci and other organisms among the infants. The American Academy of Pediatrics has established a Section on Military Pediatrics, and this specialty should be recognized by the Armed Services as being equal in importance to surgery and medicine.[5]

## CHANGING CONCEPTS OF PEDIATRIC TEACHING

Most of us who are teaching pediatrics to students and house officers realize that instead of emphasizing the diagnosis and treatment of the 346 pediatric diseases, we should stress their prevention. The present reduction in mortality has been due largely to efforts to prevent pediatric diseases. If we can train our graduates to carry out immunization measures and to feed children simply and sensibly, it should be possible, with the cooperation of health departments and the public, to reduce child mortality even further. Even now, a quarter of a million American children die each year. *Three fourths of these deaths can and should be prevented.* The public is becoming increasingly aware of the value of child care and preventive medicine, but still needs prodding as, for example, in obtaining immunization against poliomyelitis.

Even more important, pediatric teachers must make prevention, which at first glance seems dull and routine, an interesting subject. At Duke University we have tried to develop in our students a desire to keep children well, rather than a great zest for diagnosing rare diseases. Pediatric departments must devote a greater amount of time and effort to teaching future general practitioners and pediatricians more about *well* children through the examination of school children, child guidance conferences, feeding clinics, and seminars on nutrition presented in cooperation with the dietetic department. There is an old Chinese proverb that says, "He who cures a disease may be the most skillful, but he who prevents it is the safest physician."*

When Duke Hospital was opened in 1930, diphtheria was responsible for 7 per cent of the pediatric admissions, syphilis for 6 per cent, and gonorrheal ophthalmia for 2 per cent. For the past 5 years, none of these diseases has been seen. In fact, since diphtheria immunization was made compulsory and after Dr. Thomas Parran started to eradicate syphilis by compulsory premarital and antenatal serologic tests and rapid treatment centers, diphtheria and congenital syphilis have been illegal.

## INCREASING IMPORTANCE OF OUTPATIENT CARE AND TEACHING

As preventive measures become more widespread, fewer pediatric hospital beds will be needed, but pediatric outpatient clinics will require more space, a larger percentage of the pediatric teaching hours, and better instruction. Our belief, which is contrary to the usual concept, is that outpatient teaching is more valuable than bedside teaching on the wards. Keeping children out of hospitals and treating them in a physician's office or an outpatient clinic not only affords great psychological benefits to the mother and child, but also results in enor-

*Edward H. Hume, who was at Hopkins while Dr. Schorer was a student, quoted this proverb differently in his book, *Doctors East, Doctors West:* "The superior doctor prevents sickness; The mediocre doctor attends impending sickness; The inferior doctor treats actual sickness."

mous financial savings, regardless of whether the hospital bills would be paid by the child's parents, Blue Cross, the taxpayers, or university endowments. If more visiting nurses were available for home care, an even larger percentage of pediatric patients could be treated in the office or outpatient clinic, and the number of pediatric hospital beds could be reduced even further.

Home care and delay are still dangerous for children with stiff necks, "acute abdomens," and respiratory obstructions (especially if the child is under 2 years of age), and for the increasing tide of poisoning and other accidents, the greatest killers of all. Hospital care will always be needed for newborn and premature infants, for the children of working mothers, and for those suffering from conditions which can be cured only by operation. Other conditions which often necessitate hospitalization for children are cancer (including leukemia), which now ranks second among the fatal diseases of childhood, congenital heart disease, and rheumatic fever (which kills so many children between the ages of 5 and 14 years). Practically every other condition seen in pediatric practice can be, and should be, treated in a physician's office or an outpatient clinic.[6]

## THE MAINTENANCE OF PHYSICAL AND EMOTIONAL HEALTH IN CHILDHOOD

As family physicians and pediatricians become less and less occupied with physical disease, they are or should be more and more concerned with growth and physical development, with school and social activities, and with counseling on heredity and child behavior. Parents and physicians are becoming increasingly aware that the child's total development, adjustment, behavior, and his or her psychological problems from birth through adolescence are of paramount importance in the reduction of juvenile delinquency. More attention is also being focused on the rehabilitation and re-education of children with chronic conditions such as cardiac and orthopedic defects, cerebral palsy, and metabolic and allergic disorders. The child is regarded no longer merely as the site of a disease, but as a human being with family and environmental problems. On routine visits to their family doctors or pediatricians or to child welfare and outpatient clinics, the children and their mothers receive, in addition to preventive measures and health counseling, advice on many everyday problems, especially on accident prevention. In other words, continuing and comprehensive medical care is now available to children as it soon will be for adults.[7]

As a result of the increasing interest in child-family relationships, the pediatricians and psychiatrists have persuaded many obstetricians and nurses that "rooming-in" arrangements, allowing the newborn infant to be kept in constant contact with his mother from the morning after delivery, are preferable to the usual hospital nursery, in which behavior problems and serious infections may develop.[8] Physicians are also recognizing the value of closer child-family relationships when an older child must be hospitalized, and in many hospitals the parents are no longer limited to visiting hours, but are encouraged to stay with the patient day and night in order to reduce the child's psychological reaction to the strange environment of a hospital. By sharing the nursing load, parents are increasing their knowledge of child care and are helping to alleviate the increasing shortage of nurses. In many hospitals, this latter consideration has converted the nursing and administrative staffs to the desirability of having parents on the pediatric wards.

In the field of preventive psychiatry and psychosomatic medicine, social workers, nurses, teachers, pediatricians, psychologists, psychiatrists, and physicians must work together, and the ideal place is in an outpatient clinic or a physician's office. Both in private practice and in hospital outpatient clinics, the maintenance of child health has now become the major aim of pediatrics, more important than the diagnosis and treatment of disease. It is a portent of the future that the late Sir James Spence was made

Professor of Child Life at Newcastle rather than a Professor of Pediatrics.[9]

## CONCLUSION

As a result of the closer relationship between pediatrics and preventive medicine, more progress has been made in child care during the past generation than during the preceding 2,000 years. Although child health seems to have reached a golden age, there is still room for progress. The aim of pediatrics must be not only to maintain and improve the physical health of children, but, even more important, to find and use better methods for preserving their mental and emotional well-being. At the present rate, 1 of every 12 American children will spend some part of his or her life in a psychiatric institution.[10]

Except for their reluctance to use BCG, the members of all branches of the medical profession have cooperated with these pediatric efforts in preventive medicine. The accusation made by Lady Mary Wortley Montagu against our predecessors in 1717 is as unjust today as it was then:

> I am patriot enough to take pains to bring this useful invention [smallpox inoculation] into fashion in England, and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue, for the good of mankind. But that distemper [smallpox] is too beneficial to them, not to expose to all their resentment, the hardy weight that should undertake to put an end to it. Perhaps, if I live to return, I may, however, have courage to war with them. Upon this occasion, admire the heroism in the heart of
>
> Your friend,
>
> Mary Wortley Montagu.[11]

W. C. DAVISON, M.D.
DUKE UNIVERSITY MEDICAL CENTER

## REFERENCES

1. Select observations on English bodies: or, Cures both empericall and historicall, performed upon very eminent persons in desperate diseases. First, written in Latine by Mr. John Hall physician, living at Stratford upon Avon . . . Now put into English for common benefit by James Cooke practitioner in physick and chirurgery, London, 1657, Printed for John Shirley.
2. Hopkins, F. G.: The Analyst and the Medical Man, Analyst **31:** 385, 1906.
   Cooper, E. A., and Funk, Casimir: Experiments on the Causation of Beri-Beri, Lancet **2:** 1266, 1911.
   Funk, Casimir: On the Chemical Nature of the Substance Which Cures Polyneuritis in Birds Induced by a Diet of Polished Rice, J. Physiol **43:** 395, 1912; J. State Med. **20:** 341, 1912; Ergeb. d. Physiol. **13:** 126, 1913; Biochem. Bull. **4:** 304, 1915.
   Hopkins, F. G.: Feeding Experiments Illustrating the Importance of Accessory Factors in Normal Dietaries, J. Physiol. **44:** 425, 1912.
3. Telfer, L. M., Bruce, and Davison, W. C.: Progress in Child Health, North Carolina M. J. **19:** 452, 1958.
4. Davison, W. C.: The Advantages of BCG Vaccination in Preventing Tuberculosis, Quart. Rev. Pediat. & Neurol. **13:** 131, 1958.
5. Davison, W. C.: Reduction of Communicable Disease Among Troops and Children During the National Defense Program, War Med. **1:** 863, 1941.
6. Sherwood, M. M., and Davison, W. C.: The Pediatric Shift, J. PEDIAT. **40:** 536, 1952.
7. Sherwood, M. M., and Davison, W. C.: Compleat, Continuing, Comprehensive, and Total Medical Care, Supervision, and Psychological, Social, and Vocational Rehabilitation (correspondence), J. PEDIAT. **51:** 486, 1957.
   Merritt, D. H., and Davison, W. C.: Chronic Diseases in Children, in Wohl, M. G., editor: Long-Term Illness, Management of the Chronically Ill Patient, Philadelphia, 1959, W. B. Saunders Company, pp. 619-659.
8. McBryde, Angus, and Davison, W. C.: Rooming-In, North Carolina M. J. **16:** 159, 1955.
9. The Purpose and Practice of Medicine; Selections from the Writings of Sir James Spence With a Memoir by Sir John Charles, London, 1960, Oxford University Press.
10. Braceland, F. J.: Cited by Time Magazine **65:** 48 (Mar. 21), 1955.
11. Quotation From a Letter of the Right Honorable Lady Mary Wortley Montagu, London, printed from T. Beckett and P. A. DeHondt, on the Strand, 1763, vol. 2, pp. 62-63.